

Quality assurance of pharmaceuticals: a compendium of guidelines and related materials

Tenth Edition • Volume 2
Good manufacturing practices and inspection



**World Health
Organization**

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(Quality assurance of pharmaceuticals: a compendium of guidelines and related materials, tenth edition. Volume 1 – Volume 2. Good manufacturing practices and inspection)

This is the tenth edition of the second volume of the first edition entitled "*Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Volume 2. Good manufacturing practices and inspection*" published in 1999. The first three editions are available in IRIS, while the remaining editions are available electronically (CD-ROM/USB). A complete list of all previous editions in Volume 2, including these interceding electronic editions, can be found listed in the table on the next page.

ISBN 978-92-4-008608-1 (electronic version)

ISBN 978-92-4-008609-8 (print version)

ISBN 978-92-4-008663-0 (ePub version)

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Suggested citation. Quality assurance of pharmaceuticals: a compendium of guidelines and related materials, tenth edition. Volume 2. Good manufacturing practices and inspection. Geneva: World Health Organization; 2023 (Quality assurance of pharmaceuticals: a compendium of guidelines and related materials). Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at <https://iris.who.int/>.

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List of all previous QA compendiums

Edition	Title	Volumes	Format
9 th edition	Quality assurance of pharmaceuticals [electronic resource]: WHO guidelines, good practices, related regulatory guidance and GXP training materials - 2019 edition.	NA	Electronic (CD-ROM/USB)
8 th edition	Quality assurance of pharmaceuticals [electronic resource]: WHO guidelines, good practices, related regulatory guidance and GXP training materials - 2018 edition. ISBN 978-92-4-155031-4	NA	Electronic (CD-ROM/USB)
7 th edition	Quality assurance of pharmaceuticals [electronic resource]: WHO guidelines, good practices, related regulatory guidance and GXP training materials - 2017 edition.	NA	Electronic (CD-ROM/USB)
6 th edition	Quality assurance of pharmaceuticals [electronic resource]: WHO guidelines, good practices, related regulatory guidance and GXP training materials - 2016 edition.	NA	Electronic (CD-ROM/USB)
5 th edition	Quality assurance of pharmaceuticals [electronic resource]: WHO guidelines, good practices, related regulatory guidance and GXP training materials - 2015 edition.	NA	Electronic (CD-ROM/USB)
4 th edition	Quality assurance of pharmaceuticals [electronic resource]: WHO guidelines, good practices, related regulatory guidance and GXP training materials - 2014 edition.	NA	Electronic (CD-ROM/USB)
3 rd edition	Quality assurance of pharmaceuticals [electronic resource]: WHO guidelines, good practices, related regulatory guidance and GXP training materials - 2013 edition.	NA	Electronic (CD-ROM/USB)
2 nd edition (update)	Volume 2 (update) 2011 electronic version/CD-ROM: Quality assurance of pharmaceuticals [electronic resource]: a compendium of guidelines and related materials - updated 2011 ed	NA	Electronic (CD-ROM/USB)
2 nd edition	Volume 2, second edition (2007) Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 2, Good manufacturing practices and inspection (who.int)	2	PDF/print
1 st edition (update)	Volume 2 (2004) including updates, it is unclear which edition this is: Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 2 (including updates), Good manufacturing practices and inspection (who.int)	2	PDF/print
1 st edition	Volume 2 (1999) Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 2, Good manufacturing practices and inspection (who.int). This one is not OCR-ized and therefore not searchable.	2	PDF/print

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Foreword

I am pleased to introduce the new edition of the Good Manufacturing Practices (GMP) Compendium for Medical Products. This publication guides the manufacturing and quality control of pharmaceuticals, vaccines and other biologicals, and other medical products to ensure their quality, safety, and efficacy.

The importance of GMP cannot be overstated. High-quality medical products are essential for the prevention and treatment of diseases and for improving the overall health and well-being of all people of all ages without leaving anyone behind. Poor-quality products, on the other hand, can lead to adverse effects, treatment failure, and even death. The recent deaths of children in The Gambia, Indonesia and Uzbekistan due to contamination of cough syrups should not be allowed to happen again because these are preventable deaths.

The GMP Compendium for Medical Products is a valuable resource for manufacturers, regulators, and other stakeholders involved in producing and distributing medical products. It covers various topics, from quality management systems to personnel hygiene, equipment validation, and complaint handling. The guidance provided is based on the latest scientific and technical knowledge and considers the evolving regulatory landscape and the challenges faced by the industry.

This Compendium was developed by a team of experts from WHO, Member States, our Expert Advisory Panels and Expert Committees on Pharmaceutical Preparations and Biological Standardizations, as well as other organizations. It has undergone extensive consultation with stakeholders worldwide. Reflecting the collective wisdom and experience of the global community, it provides a framework for ensuring the quality of medical products in all settings.

However, the Compendium is not a static document. It needs to be regularly updated to reflect new developments in science, technology, and regulations, as well as emerging threats to public health. WHO is committed to working with its experts and partners to ensure that the Compendium remains relevant and effective in addressing the challenges of the 21st century.

I express my gratitude to all those who have contributed their time, effort, expertise and financial resources to the development of this Compendium and to encourage its widespread use by manufacturers, regulators, and other stakeholders. Together, we can ensure that medical products of the highest quality are available to all those who need them, wherever they live and regardless of their economic status.



A handwritten signature in blue ink that reads "Yukiko Nakatani". The signature is fluid and cursive, with "Yukiko" on the first line and "Nakatani" on the second line.

Dr Yukiko Nakatani,
Assistant Director-General
Access to Medicine and Health Products
World Health Organization

Acknowledgements

This publication, which is based on the reports of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, was produced by the Norms and Standards for Pharmaceuticals team of the World Health Organization (WHO), Geneva, Switzerland.

Acknowledgments are due to all those who contributed to the original reports, as well as to Mr Y. Cao, Deputy Director of the 4th Inspections Division, Centre for Food and Drug Inspection of National Medical Products Administration, Beijing, China; Dr M.A. Desouky, Senior Inspector Pharmacist and Quality Coordinator, Central Administration of Pharmaceutical Affairs, Ministry of Health, Cairo, Egypt; Mrs D. Nel, Medicines Control Officer, South African Health Products Regulatory Authority, Pretoria, South Africa; Dr L. Stoppa, Senior GMP Inspector, Inspections and Certifications Department, Manufacturing Authorisation Office, Italian Medicines Agency, Rome, Italy, Mr M. Freitas Dias, Technical Officer, WHO Regional Office for the Americas; Mr D. Mubangizi, Unit Head, WHO Prequalification; Dr D. Catsoulacos, Technical Officer, WHO Prequalification - Inspection Services; Ms S. Croft, Technical Officer WHO Prequalification - Inspection Services; Mr V. Sachdeva, Technical Officer, WHO Prequalification - Inspection Services; Dr X. Chen, Technical Officer, WHO Prequalification - Inspection Services; Dr L. Gwaza, Team Lead, WHO Norms and Standards for Pharmaceuticals; Dr S. Estevão Cordeiro, Technical Officer, WHO Norms and Standards for Pharmaceuticals and Ms. B. Kibret, Assistant to Team, WHO Norms and Standards for Pharmaceuticals , who contributed to the preparation of this publication.

WHO would like to thank the Federal Government of Germany and the United Nations Development Programme for the financial support towards the development and production costs for this publication.

Abbreviations and acronyms

3S	smart safety surveillance
ACT	Access to COVID-19 Tools
ALCOA	attributable, legible, contemporaneous, original and accurate
AMR	antimicrobial resistance
AMRH	African Medicines Regulatory Harmonization Initiative
AMRO	WHO Regional Office for the Americas
APEC	Asia-Pacific Economic Cooperation
API	active pharmaceutical ingredient
APIMF	active pharmaceutical ingredient master file
AQL	acceptance quality level
ASEAN	Association of Southeast Asian Nations
ATMP	Advanced Therapy Medicinal Product
AUC	area under the curve
AUDA-NEPAD	African Union Development Agency-New Partnership for Africa's Development
AWaRe	access, watch and reserve
BCS	Biopharmaceutics Classification System
BE	bioequivalence
BMDL	benchmark dose level
BPW	bulk purified water
BWFI	bulk water for injection
CAPA	corrective and preventive action
CpK	process capability
CPP	certificate of a pharmaceutical product
CRP Lite	collaborative registration procedure-Lite
CRS	chemical reference substance
DABT	Diplomate of the American Board of Toxicology
DAD	diode array detector

DIRA	data integrity risk assessment
EAP	WHO Expert Advisory Panel on The International Pharmacopoeia and Pharmaceutical
ECBS	Expert Committee on Biological Standardization
EC-EML	Expert Committee on the Selection and Use of Essential Medicines
ECSPP	Expert Committee on Specifications for Pharmaceutical Preparations
eCTD	electronic Common Technical Document
EDI	electro-deionization
EDQM	European Directorate for the Quality of Medicines and Healthcare
EMA	European Medicines Agency
EML	WHO Model List of Essential Medicines
EMLc	WHO Model List of Essential Medicines for Children
EOI	expression of interest
EQAAS	WHO External Quality Assurance Assessment Scheme
ERT	European Registered Toxicologist
EU	European Union
EV71	enterovirus 71
FAT	factory acceptance test
FEFO	first expiry-first out
FENSA	WHO Framework of Engagement with Non-State Actors
FPP	finished pharmaceutical product
GBT	Global Benchmarking Tool
GC	gas chromatography
GCFR	global competency framework
GCP	good clinical practices
GDP	good distribution practices
GLP	good laboratory practices
GMP	good manufacturing practices
GPW13	WHO's 13th General Programme of Work

GRelP	good reliance practices
GRP	good regulatory practices
GTDP	good trade and distribution practices
GVP	good pharmacovigilance practices
GxP	good practices
HBEL	health-based exposure limit
HPLC	high-performance liquid chromatography
HPS	Health Products Policy and Standards (WHO department)
HVAC	heating, ventilation and air-conditioning
IAEA	International Atomic Energy Agency
IAU	Innovation, Access and Use (WHO team)
ICDRA	International Conferences of Drug Regulatory Authorities
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICRS	International Chemical Reference Substances
IEC	International Electrotechnical Commission
IMP	investigational medical products
IMWP	International Meeting of World Pharmacopoeias
INN	International Nonproprietary Names
IQ	installation qualification
ISO	International Organization for Standardisation
LC	liquid chromatography
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
mAb	monoclonal antibody
MDR-TB	multidrug-resistant tuberculosis
MHRA	Medicines & Healthcare Products Regulatory Agency
MKT	mean kinetic temperature
mRNA	messenger ribonucleic acid

MSC	maximum safe carryover
MSM	Member State Mechanism
MSSR	maximum safe surface residue
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRA	national regulatory authority
NSP	Norms and Standards for Pharmaceuticals (WHO team)
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
OMCLs	official medicine control laboratories
OQ	operational qualification
PAHO	Pan American Health Organization
PDE	permissible daily exposure
PDE	permitted daily exposure
PDG	Pharmacopoeial Discussion Group
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PQCL	pharmaceutical quality control laboratory
PQT	WHO Prequalification Team
PQT/INS	WHO Prequalification Team for Inspection Services
PQT/MED	WHO Prequalification Team for Medicines Assessment
PVDC	polyvinylidene chloride
PVDF	polyvinylidene difluoride
Q&A	question and answer
QA	quality assurance
QCL	quality control laboratory
QMS	quality management system
QRM	quality risk management
QSE	quality, safety and efficacy
R&D	research and development

RHT	Regulation of Medicines and Other Health Technologies (unit)
RO	reverse osmosis
rpm	rotations per minute
RSS	Regulatory System Strengthening (WHO team)
SAT	site acceptance test
SDGs	Sustainable Development Goals
SF	substandard and falsified
SoINN	School of International Nonproprietary Names
SOP	standard operating procedure
SPC	statistical process control
SmPC	summary of product characteristics
SRA	stringent regulatory authority
TB	tuberculosis
TLC	thin-layer chromatography
TOC	total organic carbon
UN	United Nations
UNEP	United Nations Environment Programme
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
URS	user requirement specifications
USA	United States of America
USFDA	United States Food and Drug Administration
UV	ultraviolet
VRL	visible residue limit
WFI	water for injection
WHO	World Health Organization
WLA	WHO-listed authority
WPU	water for pharmaceutical use

Executive summary

The World Health Organization (WHO) developed the Quality Assurance of Pharmaceuticals Compendium, Volume 2, to ensure the quality, safety and effectiveness of medicines, focusing on good manufacturing practices (GMP) and related guidelines. This summary provides an overview of the key features and updates in the latest edition.

The Compendium is a valuable tool for countries to establish robust regulatory systems and uphold international standards in pharmaceutical quality assurance. It consolidates essential recommendations and guidelines related to GMP in a structured manner, facilitating easy access to vital information.

Despite global efforts to ensure the availability of quality medicines, substandard and falsified products still pose challenges in healthcare delivery in many countries. To address this issue, WHO's Expert Committee on Specifications for Pharmaceutical Preparations has made numerous recommendations to establish standards, guidelines and promote effective regulatory and control systems.

The GMP Compendium for Medical Products guides the manufacturing and quality control of pharmaceuticals, vaccines, biologicals and other medical products. It aims to ensure the quality, safety and efficacy of these products which are crucial for preventing and treating diseases and improving global health.

The latest edition of the Compendium features several updates and new texts to ensure the recommendations are fit-for-purpose and current. It now includes forty-five guidelines covering topics related to GMP and the inspection of pharmaceutical manufacturers and distribution channels. Among these guidelines, ten have been revised to incorporate the latest advancements and address emerging challenges in the pharmaceutical industry, while eight new guidelines have been introduced to address previously unexplored areas. These new topics include GMP for investigational radiopharmaceuticals and medicinal gases, recommendations on environmental aspects for the prevention of antimicrobial resistance, health-based exposure limits in cleaning validation and good practices for research and development facilities.

The Compendium is organized into sections: GMP main principles, starting materials, specific medical products, related guidelines, laboratory guidelines and inspections. Each section offers detailed advice and comprehensive coverage of pharmaceutical quality assurance.

The guidelines within the Compendium align with internationally recognized texts and establish acceptable international standards. However, they allow for necessary adaptations to address unique conditions in individual countries as long as deviations are validated for equivalence.

Emphasizing the importance of inspections in enforcing GMP compliance, licensing and maintaining product quality throughout distribution channels, the Compendium helps combat the challenges posed by substandard and falsified medicines. It provides guidance on inspecting manufacturing facilities, drug distribution channels

and conducting pre-approval inspections. Furthermore, it highlights the growing significance of implementing quality systems not only in pharmaceutical manufacturing facilities but also within pharmaceutical inspectorates.

The tenth edition of the GMP Compendium builds upon the success of the previous edition, incorporating revised guidelines to reflect the latest developments and introducing new guidelines to address emerging needs. It is an indispensable resource for regulatory authorities, pharmaceutical manufacturers and other stakeholders involved in ensuring the quality, safety, and efficacy of pharmaceutical products.

Introduction

Quality Assurance of Pharmaceuticals: a Compendium of Guidelines and Related Materials, Volume 2, serves as a comprehensive resource for ensuring the quality, safety and efficacy of medicines. This publication consolidates the essential recommendations and guidelines of the World Health Organization (WHO) related to good manufacturing practices (GMP) and inspections, in a structured manner and within one publication. In addition, it aims to support countries in setting up robust regulatory systems and upholding international standards in pharmaceutical quality assurance to combat substandard and falsified medicines.

From its inception, the WHO committed to address the quality assurance of medicines. Article 2 of the Constitution mandates that WHO develop and promote international standards for food, biologicals, pharmaceuticals and related products. Global standards are essential to ensure the development, manufacture, storage, distribution and use of quality, safe and effective medicines worldwide.

Over time, the World Health Assembly has adopted multiple resolutions urging WHO to develop international standards, recommendations and instruments for assuring the quality of medicines produced and traded both nationally and internationally. In response, the WHO Expert Committee on Specifications for Pharmaceutical Preparations has made several recommendations on quality assurance and control. However, these recommendations were published separately in various technical reports, making it challenging for users to perceive them as a cohesive system, accessing and implementing the relevant WHO guidelines.

To address these challenges, the Compendium serves as a centralized, continuously updated resource for regulators, healthcare professionals, industry experts and other stakeholders. Designed as a 'one-stop-shop,' this publication eliminates the need to consult multiple texts by consolidating all existing and newly updated WHO guidelines, recommendations and annexes into a single, comprehensive document. Further enhancing its utility, the Compendium arranges these texts in a logical manner that reflects their application in real-world settings, thereby simplifying access and interpretation. As a result, users will find it easier to implement WHO's guidelines quickly and effectively. This publication serves as an indispensable, logically organized and regularly updated resource that simplifies and harmonizes the approach to pharmaceutical quality assurance and control.

The Compendium consists of two volumes. Volume 1, initially published in 1997, focuses on regulatory systems, product development, registration, quality control, distribution and related regulatory standards. Volume 2, first published in 1999, centers around good manufacturing practices (GMP) and the inspection of pharmaceutical manufacturers and distribution channels. GMP is a critical part of quality assurance and serves as the technical standard for the WHO Certification Scheme on the Quality of Pharmaceutical Products in International Commerce.

Overview of the good manufacturing practices Compendium

The GMP guidelines have evolved since their first publication in the late 1960s, with subsequent updates and additions addressing specific aspects and specialized areas of pharmaceutical manufacturing. These guidelines encompass various pharmaceutical products, including investigational products and radiopharmaceuticals. Each set of guidelines is tailored to address the specific requirements and challenges associated with the respective products.

Inspections play a vital role in enforcing GMP compliance, licensing and ensuring the quality of pharmaceutical products throughout the distribution channels. The guidelines included in this Compendium provide detailed advice on inspecting manufacturing facilities and distribution channels and conducting pre-approval inspections. Additionally, the publication highlights the increasing importance of implementing quality systems in pharmaceutical inspectorates and offers guidance on this subject.

The guidelines set forth by WHO for GMP align with internationally recognized texts. While they establish acceptable and appropriate international standards, their advisory nature allows for necessary adaptations to address specific conditions in individual countries. However, any departure from recommended practices should be validated for equivalence.

Structure of the good manufacturing practices Compendium

The Compendium is divided into sections, covering GMP principles, starting materials, specific medical products, related guidelines, laboratory guidelines, inspections and further reading. Each section provides valuable guidance in its respective domain and ensures comprehensive coverage of pharmaceutical quality assurance.

WHO good manufacturing practices: main principles for pharmaceutical products

This section provides the key documents published in the WHO Technical Report Series that outline the main principles and specific considerations related to GMP for pharmaceutical products. These considerations include various aspects of pharmaceutical manufacturing, including validation, water for pharmaceutical use, production of water for injection and heating, ventilation and air-conditioning (HVAC) systems. The main GMP principles outline the fundamental requirements for manufacturing processes, facilities, quality control and quality assurance to ensure the consistent production of quality, safe and effective pharmaceuticals.

This section includes GMP requirements for producing, storing and distributing water for pharmaceutical use in bulk form produced by distillation or means other than distillation. Also, Annex 3 of the 2021 Technical Report Series covers the production of

water for injection by means other than distillation. This document presents alternative methods for producing high-quality water for injection, providing manufacturers with options that meet the necessary standards while considering practical and cost-effective approaches.

This section also includes requirements for HVAC systems in non-sterile pharmaceutical manufacturing. Annex 8 (2018) provides guidelines for designing, installing, operating and maintaining HVAC systems, emphasizing the need for adequate air quality control to prevent contamination and maintain product integrity. Annex 2 (2019) supplements these guidelines by interpreting the HVAC system guidelines. Guidelines on validation offer comprehensive guidance on the validation of pharmaceutical manufacturing processes, analytical methods and computerized systems, emphasizing the need for robust and reliable validation practices to guarantee product quality and compliance with regulatory requirements. This section also includes points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation, highlighting the significance of establishing appropriate cleaning validation protocols based on health risk assessments to prevent cross-contamination and ensure product safety.

WHO good manufacturing practices: starting materials

Section 2 covers the GMP for starting materials; these texts remain unchanged since the last GMP compendium in 2019. The section has two texts: one for active pharmaceutical ingredients (bulk drug substances) and another for pharmaceutical excipients. As the strict application of full GMP is not always practical or necessary for such materials, these texts outline the procedures and practices that manufacturers should employ to ensure that the methods, facilities and controls used for their production are operated or managed so that pharmaceutical starting materials have the quality and purity appropriate for use in finished pharmaceutical products. The GMP text for pharmaceutical excipients is under revision and will be updated in the next version of the compendium.

WHO good manufacturing practices: specific medical products

This section encompasses a range of guidelines that focus on ensuring the quality, safety and efficacy of specific categories of medical products. These guidelines address the unique manufacturing requirements and challenges associated with pharmaceutical products containing hazardous substances, sterile pharmaceutical products, biological products, blood establishments, investigational products, herbal medicines, radiopharmaceutical products, investigational radiopharmaceutical products and medicinal gases. By providing detailed recommendations, these guidelines enable manufacturers to establish and maintain robust manufacturing processes, quality control measures and facility requirements specific to each category. The guidelines are developed in collaboration with expert committees, such as the Expert Committee on

Biological Standardization (for blood establishments and biological products) and the International Atomic Energy Agency (IAEA) (for radiopharmaceuticals), to ensure a comprehensive and science-based approach. Implementing these guidelines facilitates the production of high-quality medical products that meet international standards, contributing to the safety and efficacy of healthcare interventions and patient well-being.

Related guidelines

The "Related guidelines" section includes a diverse collection of guidelines that cover various aspects related to pharmaceutical manufacturing, research and development, data integrity, environmental considerations, risk management, technology transfer, storage and distribution practices, trade and distribution practices, sampling, certification schemes, packaging, documentation and stability testing. These guidelines provide valuable guidance to ensure pharmaceutical products' quality, safety and integrity throughout their life cycle. They address critical areas such as research and development facilities, hold-time studies, data integrity, prevention of antimicrobial resistance, quality risk management, technology transfer, herbal processing practices, storage and distribution practices, trade and distribution practices for starting materials, sampling, certification schemes, packaging, site master files, contract research organization master files, storage and transport of time- and temperature-sensitive pharmaceutical products, stability testing of active pharmaceutical ingredients and finished products. By following these guidelines, manufacturers, regulators and stakeholders in the pharmaceutical industry can enhance their practices and processes, contributing to the production of safe and effective medicines and ensuring the integrity of the pharmaceutical supply chain.

Inspection

Inspections are vital in assessing compliance with GMP, quality management systems and regulatory requirements. This section includes various guidelines and recommendations that guide conducting inspections and evaluating compliance in several aspects of the pharmaceutical industry. The guidelines address various levels and types of inspections, starting with national inspectorates' quality management system requirements. These requirements provide a framework for setting up and maintaining effective inspection systems within national regulatory authorities. The section also covers the inspection of pharmaceutical manufacturers, first addressed in Annex 2 of the WHO Technical Report Series in 1992, by outlining the essential aspects to be considered during inspections of manufacturing facilities, ensuring compliance with GMP standards and regulatory requirements.

The Compendium includes a model inspection report and an example of a risk category assessment in Annex 4, Appendix 1 and Appendix 2 to help inspections and provide standardized approaches. These resources help inspectors in conducting thorough assessments and categorizing sites based on compliance levels.

Pre-approval inspections, another crucial aspect of the inspection process, are covered in Annex 7 of the WHO Technical Report Series published in 2002. These guidelines provide specific guidance on inspections conducted before granting marketing authorization for new pharmaceutical products, ensuring compliance with GMP principles.

Furthermore, the Compendium addresses compliance with GMP, good laboratory practices (GLP) and good clinical practices (GCP) through desk assessments. This guidance, provided in Annex 9 of the WHO Technical Report Series published in 2018, offers a systematic approach for evaluating compliance without conducting on-site physical inspections.

Lastly, the Compendium includes the model quality assurance system for procurement agencies, outlined in Annex 4 of the WHO Technical Report Series published in 2014. This guideline serves as an aide-memoire for inspection activities by procurement agencies to ensure the quality and integrity of the products they procure.

Laboratory guidelines

The guidelines in this section guide pharmaceutical control laboratories working in a GMP environment on how to work in a safe and effective manner to ensure the quality of pharmaceutical products. The purposes of these guidelines are to promote the quality of pharmaceutical products by ensuring that pharmaceutical control laboratories are working to high standards, facilitate the international trade in pharmaceutical products by providing a common set of standards for pharmaceutical control laboratories and provide a basis for the assessment of pharmaceutical control laboratories by regulatory authorities.

The good practices for quality control laboratories cover all aspects of pharmaceutical quality control, including organization and management, personnel, premises and equipment, documentation and records, operating procedures, internal quality control and external quality assurance. The guidance on microbiology laboratories provides specific guidance on the quality control of pharmaceutical products for microbiological contamination. The laboratory information file guides how to prepare a laboratory information file which is a document that describes the laboratory's organization, personnel, facilities, equipment and procedures.

Changes in the tenth edition

The Revision History at the end of this document provides an overview of the main changes in the tenth edition of the GMP Compendium. The tenth edition of the Compendium has 45 WHO GMP guidelines and related texts, of which eight are new guidelines published for the first time, ten are revisions or updates of existing guidelines and the rest remain unchanged from the ninth edition.

Revisions and updates to published WHO guidelines

Since the last publication, the GMP for water for pharmaceutical use, radiopharmaceuticals, investigational products and sterile pharmaceutical products, and validation were revised and updated. The GMP for sterile pharmaceutical products is a harmonized text developed in collaboration with the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/s), the European Commission and the European Medicines Agency (EMA). Other GMP-related texts that were revised and updated are quality management system requirements for national inspectorates, good storage and distribution practices for medical products, data integrity, technology transfer in pharmaceutical manufacturing and the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. WHO continues to monitor published guidelines and update them as necessary to ensure the requirements are still current and fit for purpose. The Compendium helps to guide users in this respect so that they always refer to the most up-to-date WHO requirements.

New WHO guidelines

Following the publication of the Guidelines on HVAC systems for non-sterile pharmaceutical products in 2018, the WHO developed an interpretation guideline to facilitate the implementation of the HVAC guidelines. This new guideline has non-binding examples, drawings, technical representations and interpretations of the HVAC systems guidelines. It is intended to be a basic and explanatory guide for use by pharmaceutical manufacturers and GMP inspectors. To supplement the validation guidelines, specifically cleaning validation (Appendix 3 in Annex 3, Technical Report Series 1019), WHO published Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation. HBELs are the levels of exposure to pharmaceutical residues that are safe for human health. A new guideline is also included in the 10th edition that provides guidance on the production of water for injection by means other than distillation.

Two new product-specific GMP guidelines that cover medicinal gases and investigational radiopharmaceuticals are included in the 10th edition. Arising from an increased demand for medicinal gases, in particular the use of oxygen in the treatment of patients with coronavirus disease 2019 (COVID-19), the GMP for medicinal gases addresses requirements for the production, control, storage and distribution of medicinal gases. This document does not cover the manufacture of medicinal gases in hospitals or at home for personal use. However, the principles contained in this document may be applied in those instances to ensure that oxygen generated at hospitals or homes is suitable for the intended use and meets the quality standards. GMP for investigational radiopharmaceuticals addresses current expectations and trends in GMP specific to investigational radiopharmaceuticals used in clinical trials (that is, phase I, phase II and phase III trials) and to harmonize the text with the principles from other related international guidelines.

Another new guideline on good chromatography practices highlights good practices to be considered in the analysis of samples when chromatographic methods and systems are used. The principles should be applied in the analysis of, for example, raw materials, starting materials, intermediates, in-process materials and finished products.

Two GMP-related guidelines are included in the 10th edition, addressing important issues on antimicrobial resistance and GMP requirements for research and development facilities. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance outline key considerations for both manufacturers and inspectors focused on mitigating antimicrobial resistance through better waste management in pharmaceutical facilities. It aims to educate stakeholders, including manufacturers and regulatory authorities, on relevant waste management aspects of GMP. The good practices for research and development facilities of pharmaceutical products address the production and control of preclinical and not-for-human-use batches manufactured in pharmaceutical formulation and development facilities, where these are directly supporting, for example, shelf-life claims, animal studies or validation activities.

In conclusion, Volume 2 of Quality Assurance of Pharmaceuticals: a Compendium of Guidelines and Related Materials is a comprehensive resource for pharmaceutical quality assurance. It combines essential recommendations, guidelines and other materials in a structured manner to support countries in ensuring the quality, safety and efficacy of medicines. An alphabetical index of subjects covered in Volume 2 of Quality Assurance of Pharmaceuticals: a Compendium of Guidelines and Related Materials is included at the end of this volume.

1. WHO good manufacturing practices: main principles for pharmaceutical products

1.1 WHO good manufacturing practices for pharmaceutical products: main principles¹

Annex 2, WHO Technical Report Series, 986,
2014

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¹ The current document is a revision of WHO Good manufacturing practices for pharmaceutical products: main principles, previously published in WHO Technical Report Series, No. 961, 2011, Annex 3.

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Introduction

The first WHO draft text on good manufacturing practices (GMP) was prepared in 1967 by a group of consultants at the request of the Twentieth World Health Assembly (resolution WHA20.34). It was subsequently submitted to the Twenty-first World Health Assembly under the title *Draft requirements for good manufacturing practice in the manufacture and quality control of medicines and pharmaceutical specialities* and was accepted.

The revised text was discussed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1968 and published as an annex to its twenty-second report. The text was then reproduced (with some revisions) in 1971 in the Supplement to the second edition of *The International Pharmacopoeia*.

In 1969, when the World Health Assembly recommended the first version of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce in resolution WHA22.50, it accepted at the same time the GMP text as an integral part of the Scheme. Revised versions of both the Certification Scheme and the GMP text were adopted in 1975 by resolution WHA28.65. Since then, the Certification Scheme has been extended to include the certification of:

- veterinary products administered to food-producing animals;
- starting materials for use in dosage forms, when they are subject to control by legislation in both the exporting Member State and the importing Member State;
- information on safety and efficacy (resolution WHA41.18, 1988).

In 1992, the revised draft requirements for GMP were presented in three parts, of which only parts 1 and 2 are reproduced in this document (1). “Quality management in the medicines industry: philosophy and essential elements”, outlines the general concepts of quality assurance (QA) as well as the principal components or subsystems of GMP, which are joint responsibilities of top management and of production and quality control management. These include hygiene, validation, self-inspection, personnel, premises, equipment, materials and documentation.

“Good practices in production and quality control”, provides guidance on actions to be taken separately by production and by quality control personnel for the implementation of the general principles of QA.

These two parts were subsequently supplemented by further guidelines which are integral parts of these GMP for pharmaceutical products.

Considerable developments in GMP have taken place in the intervening years, and important national and international documents, including new revisions, have appeared (2–5). Thus there is a necessity to revise the main principles and incorporate the concept of validation.

Among other items of feedback discussed during the consultation on WHO guidelines for medicines quality assurance, quality control (QC) laboratories and transfer of technology on 27–31 July 2009, the need was identified to incorporate a new section on “Product quality review” under Chapter 1: “Quality assurance”.

In addition, several updates were suggested to further enhance the guidelines. These included the concept of risk management, replacing “drugs” by the term “medicines” and introducing the concept of a “quality unit”.

During 2012 the Secretariat was made aware that the current *Good manufacturing practices (GMP) for pharmaceutical products: main principles*, published as Annex 3 in the WHO Technical Report Series, No. 961, 2011, would need updating.

The WHO Expert Committee on Specifications for Pharmaceutical Preparations discussed the need for an update during its forty-seventh meeting and agreed to pursue the matter accordingly.

The following sections were updated in the newly revised version and, after the usual consultation process, were presented to the forty-eighth Expert Committee for adoption:

- Section: **Pharmaceutical quality system**
- Section 2: **2. Good manufacturing practices for pharmaceutical products**
- Section 7: **Contract production, analysis and other activities**
- Section 17: **17. Good practices in quality control**

General considerations

Licensed pharmaceutical products (marketing authorization) should be manufactured only by licensed manufacturers (holders of a manufacturing authorization) whose activities are regularly inspected by competent national authorities. This guide to GMP shall be used as a standard to justify GMP status, which constitutes one of the elements of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce, through the assessment of applications for manufacturing authorizations and as a basis for the inspection of manufacturing facilities. It may also be used as training material for government medicines inspectors, as well as for production, QC and QA personnel in the industry.

The guide is applicable to operations for the manufacture of medicines in their finished dosage forms, including large-scale processes in hospitals and the preparation of supplies for use in clinical trials.

The good practices outlined below are to be considered general guides,² and they may be adapted to meet individual needs. The equivalence of alternative approaches to

² The word “should” in the text means a strong recommendation.

QA, however, should be validated. The guide as a whole does not cover safety aspects for the personnel engaged in manufacture, or environmental protection: these are normally governed by national legislation. A new concept of hazard analysis related to the risks in production and personnel safety has also been recently recommended (WHO Technical Report Series, No. 961, Annex 7). The manufacturer should assure the safety of workers and take the necessary measures to prevent pollution of the external environment.

International Nonproprietary Names (INN) for pharmaceutical substances designated by WHO should be used when available, together with other designated names.

Glossary

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

active pharmaceutical ingredient (API). Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

airlock. An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for use either by people or for goods and/or equipment.

authorized person. The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested and approved for release in compliance with the laws and regulations in force in that country.

batch (or lot). A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

batch number (or lot number). A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

batch records. All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

bulk product. Any product that has completed all processing stages up to, but not including, final packaging.

calibration. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

clean area. An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

consignment (or delivery). The quantity of a pharmaceutical or pharmaceuticals, made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

contamination. The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.

critical operation. An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

cross-contamination. Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

finished product. A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling.

in-process control. Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

intermediate product. Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

large-volume parenterals. Sterile solutions intended for parenteral application with a volume of 100 ml or more in one container of the finished dosage form.

manufacture. All operations of purchase of materials and products, production, quality control (QC), release, storage and distribution of pharmaceutical products, and the related controls.

manufacturer. A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

marketing authorization (product licence, registration certificate). A legal document issued by the competent medicines regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life.

master formula. A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

master record. A document or set of documents that serve as a basis for the batch documentation (blank batch record).

packaging. All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

packaging material. Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

pharmaceutical product. Any material or product intended for human or veterinary use presented in its finished dosage form, or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

production. All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

qualification. Action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results. The meaning of the word “validation” is sometimes extended to incorporate the concept of qualification.

quality assurance. See Part 1 (6).

quality control. See Part 1 (6).

quality unit(s). An organizational unit independent of production which fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

quarantine. The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

reconciliation. A comparison between the theoretical quantity and the actual quantity.

recovery. The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

reprocessing. Subjecting all or part of a batch or lot of an in-process medicine, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch or lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological medicines and, in such cases, are validated and pre-approved as part of the marketing authorization.

reworking. Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization.

self-contained area. Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well established procedures, controls and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

specification. A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

standard operating procedure (SOP). An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

starting material. Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

validation. Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

Quality management in the medicines industry: philosophy and essential elements³

In the medicines industry at large, quality management is usually defined as the aspect of the management function that determines and implements the “quality policy”, i.e. the overall intention and direction of an organization regarding quality, as formally expressed and authorized by top management. The basic elements of quality management are:

- an appropriate infrastructure or “quality system”, encompassing the organizational structure, procedures, processes and resources;
- systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality.

The totality of these actions is termed “QA”. Within an organization, QA serves as a management tool. In contractual situations, QA also serves to generate confidence in the supplier. The concepts of QA, GMP, QC and quality risk management (QRM) are interrelated aspects of quality management and should be the responsibility of all personnel. They are described here in order to emphasize their relationship and their fundamental importance to the production and control of pharmaceutical products.

1. Pharmaceutical quality system

1.1 *Principle.* The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of staff in many different departments and at all levels within the company, the company’s suppliers and the distributors. To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented pharmaceutical quality system (PQS) incorporating GMP and QRM

³ Good manufacturing practices for pharmaceutical products, Part One. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823); and in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2*, 2nd updated edition. *Good manufacturing practices and inspection*. Geneva, World Health Organization, 2007; and in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials*. Geneva, World Health Organization, 2010 (CD-ROM).

- 1.2 Senior management has the ultimate responsibility to ensure an effective PQS is in place, is adequately resourced, and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organization. Senior management's leadership and active participation in the PQS is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organization to the PQS.
- 1.3 Quality management is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality management, therefore, incorporates GMP and other factors, including those outside the scope of this guide, such as product design and development.
- 1.4 GMP applies to the life-cycle stages from the manufacture of investigational medicinal products, technology transfer, and commercial manufacturing, through to product discontinuation. The PQS can extend to the pharmaceutical development life-cycle stage and should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities. All parts of the PQS should be adequately resourced and maintained, including being provided with sufficient competent personnel, suitable premises, equipment and facilities.
- 1.5 The PQS appropriate to the manufacture of pharmaceutical products should ensure that:
 - a) product realization is achieved by designing, qualifying, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;
 - b) product and process knowledge is managed throughout all life-cycle stages;
 - c) pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of good laboratory practice (GLP) and good clinical practice (GCP);
 - d) production and control operations are clearly specified in a written form and GMP requirements are adopted;
 - e) managerial responsibilities are clearly specified in job descriptions;
 - f) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is the correct material from the approved supply chain;

- g) all necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations and validations are carried out;
- h) the finished product is correctly processed and checked, according to the defined procedures;
- i) pharmaceutical products are not sold or supplied before the authorized persons (see also sections 9.11 and 9.12) have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products;
- j) processes are in place to assure the management of outsourced activities;
- k) satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf-life;
- l) there is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the PQS;
- m) product and processes are monitored and the results taken into account in batch release, in the investigation of deviations and, with a view to taking preventive action to avoid potential deviations occurring in the future;
- n) arrangements are in place for the prospective evaluation and approval of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required.
After implementation of any change, an evaluation is undertaken to confirm that the quality objectives were achieved and that there was no unintended adverse impact on product quality;
- o) regular reviews of the quality of pharmaceutical products are conducted with the objective of verifying the consistency of the process and identifying where there is a need for improvement;
- p) a state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality;
- q) continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge;
- r) there is a system for QRM;
- s) deviations, suspected product defects and other problems are reported, investigated and recorded. An appropriate level of root cause analysis is applied during such investigations. The most likely root cause(s) should

be identified and appropriate corrective actions and/or preventive actions (CAPAs) should be identified and taken. The effectiveness of CAPAs should be monitored.

- 1.6 There should be periodic management reviews, with the involvement of senior management, of the operation of the PQS to identify opportunities for continual improvement of products, processes and the system itself. Unless otherwise justified, such reviews should be conducted at least annually.
- 1.7 The PQS should be defined and documented. A quality manual or equivalent documentation should be established and should contain a description of the quality management system including management responsibilities.

Quality risk management

- 1.8 QRM is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.
- 1.9 QRM should ensure that:
 - the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;
 - the level of effort, formality and documentation of the QRM process is commensurate with the level of risk.

Product quality review

- 1.10 Regular, periodic or rolling quality reviews of all pharmaceutical products, including export-only products, should be conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:
 - a) review of starting materials and packaging materials used for the product, especially those from new sources and in particular the review of supply chain traceability of active substances;
 - b) a review of critical in-process controls, and finished product results;
 - c) a review of all batches that failed to meet established specification(s) and their investigation;

- d) a review of all significant deviations or non-conformances, the related investigations and the effectiveness of resultant CAPAs taken;
- e) a review of all changes made to the processes or analytical methods;
- f) a review of dossier variations submitted, granted or refused;
- g) a review of the results of the stability monitoring programme and any adverse trends;
- h) a review of all quality-related returns, complaints and recalls and the investigations performed at the time;
- i) a review of adequacy of any other previous corrective actions on product processes or equipment;
- j) post-marketing commitments for new dossiers and variations to the dossiers;
- k) the qualification status of relevant equipment and utilities, e.g. heating, ventilation and air-conditioning (HVAC), water or compressed gases and a review of the results of monitoring the output of such equipment and utilities;
- l) a review of technical agreements to ensure that they are up to date.

The manufacturer and, where different, marketing authorization holder, should evaluate the results of the review and an assessment should be made as to whether CAPA or any revalidation should be undertaken, under the PQS. CAPAs should be completed in a timely and effective manner, according to documented procedures. There should be procedures for the ongoing management and review of these actions, and the effectiveness of these procedures should be verified during self-inspection. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, or sterile products, where scientifically justified. Where the marketing authorization holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The authorized person responsible for final batch certification, together with the marketing authorization holder, should ensure that the quality review is performed in a timely manner and is accurate.

2. Good manufacturing practices for pharmaceutical products

- 2.1 GMP is that part of quality management which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial authorization or product specification. GMP is concerned with both

production and QC. GMP is aimed primarily at managing and minimizing the risks inherent in pharmaceutical manufacture to ensure the quality, safety and efficacy of products. Under GMP:

- a) all manufacturing processes are clearly defined, systematically reviewed for associated risks in the light of scientific knowledge and experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;
- b) qualification and validation are performed;
- c) all necessary resources are provided, including:
 - (i) sufficient and appropriately qualified and trained personnel,
 - (ii) adequate premises and space,
 - (iii) suitable equipment and services,
 - (iv) appropriate materials, containers and labels,
 - (v) approved procedures and instructions,
 - (vi) suitable storage and transport,
 - (vii) adequate personnel, laboratories and equipment for in-process controls;
- d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;
- e) procedures are carried out correctly and personnel are trained to do so;
- f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected. Any significant deviations are fully recorded and investigated with the objective of determining the root cause and appropriate corrective and preventive action is implemented;
- g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
- h) the proper storage and distribution of the products minimizes any risk to their quality and takes account of good distribution practices (GDP);
- i) a system is available to recall any batch of product from sale or supply;
- j) complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products to prevent recurrence.

3. Sanitation and hygiene

- 3.1 A high level of sanitation and hygiene should be practised in every aspect of the manufacture of medicines. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene. (For *Personal hygiene* see section 11, and for *sanitation* see section 12, “Premises”.)

4. Qualification and validation

- 4.1 In accordance with GMP, each pharmaceutical company should identify what qualification and validation work is required to prove that the critical aspects of their particular operation are controlled.
- 4.2 The key elements of a qualification and validation programme of a company should be clearly defined and documented in a validation master plan.
- 4.3 Qualification and validation should establish and provide documentary evidence that:
- a) the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP (design qualification or DQ);
 - b) the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications (installation qualification or IQ);
 - c) the premises, supporting utilities and equipment operate in accordance with their design specifications (operational qualification or OQ);
 - d) a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (process validation or PV, also called performance qualification or PQ).
- 4.4 Any aspect of operation, including significant changes to the premises, facilities, equipment or processes, which may affect the quality of the product, directly or indirectly, should be qualified and validated.
- 4.5 Qualification and validation should not be considered as one-off exercises. An ongoing programme should follow their first implementation and should be based on an annual review.

- 4.6 The commitment to maintain continued validation status should be stated in the relevant company documentation, such as the quality manual or validation master plan.
- 4.7 The responsibility for performing validation should be clearly defined.
- 4.8 Validation studies are an essential part of GMP and should be conducted in accordance with predefined and approved protocols.
- 4.9 A written report summarizing the results recorded and the conclusions reached should be prepared and stored.
- 4.10 Processes and procedures should be established on the basis of the results of the validation performed.
- 4.11 Particular attention should be paid to the validation of analytical test methods, automated systems and cleaning procedures.

5. Complaints

- 5.1 *Principle.* All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken.
- 5.2 A person responsible for handling the complaints and deciding the measures to be taken should be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorized person, the latter should be made aware of any complaint, investigation or recall.
- 5.3 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.
- 5.4 Special attention should be given to establishing that the product that gave rise to a complaint was defective.
- 5.5 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for QC should normally be involved in the review of such investigations.
- 5.6 If a product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected. In particular, other batches that may contain reprocessed product from the defective batch should be investigated.

- 5.7 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.
- 5.8 All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
- 5.9 Complaints records should be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.
- 5.10 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, a suspect product or any other serious quality problems with a product.

6. Product recalls

- 6.1 *Principle.* There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.
- 6.2 The authorized person should be responsible for the execution and coordination of recalls. He or she should have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.
- 6.3 There should be established written procedures, which are regularly reviewed and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly down to the required level in the distribution chain.
- 6.4 An instruction should be included in the written procedures to store recalled products in a secure segregated area while their fate is decided.
- 6.5 All competent authorities of all countries to which a given product has been distributed should be promptly informed of any intention to recall the product because it is, or is suspected of being, defective.
- 6.6 The distribution records should be readily available to the authorized person, and they should contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.
- 6.7 The progress of the recall process should be monitored and recorded. Records should include the disposition of the product. A final report should be issued, including a reconciliation between the delivered and recovered quantities of the products.

- 6.8 The effectiveness of the arrangements for recalls should be tested and evaluated from time to time.

7. Contract production, analysis and other activities

- 7.1 *Principle.* Contract production, analysis and any other activity covered by GMP must be correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a product, or work or analysis, of unsatisfactory quality.

General

- 7.2 All arrangements for contract production and analysis, including technology transfer and any proposed changes in technical or other arrangements, should be in accordance with the marketing authorization for the product concerned.
- 7.3 The contract should permit the contract giver to audit the facilities and activities of the contract acceptor or mutually agreed subcontractors.
- 7.4 In the case of contract analysis, the final approval for release must be given by the authorized person in accordance with GMP and the marketing authorization as specified in the contract.

The contract giver

- 7.5 The PQS of the contract giver should include the control and review of any outsourced activities. The contract giver is responsible for assessing the legality, suitability and competence of the contract acceptor to successfully carry out the work or tests required, for approval for contract activities, and for ensuring by means of the contract that the principles of GMP incorporating QRM principles are followed.
- 7.6 The contract giver should provide the contract acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The contract giver should ensure that the contract acceptor is fully aware of any hazards associated with the product, work or tests that might pose a risk to premises, equipment, personnel, other materials or other products.
- 7.7 The contract giver should review and assess the records and results related to the outsourced activities. The contract giver should ensure that all products and materials delivered by the contract acceptor have been processed in accordance with GMP and the marketing authorization; comply with their specifications and that the product has been released by the authorized person in accordance with GMP and the marketing authorization.

- 7.8 The contract giver should monitor and review the performance of the contract acceptor including the implementation of any needed improvements and their effectiveness.
- 7.9 The contract giver is responsible for ensuring that the contract acceptor understands that his or her activities may be subject to inspection by competent authorities.

The contract acceptor

- 7.10 The contract acceptor must have adequate premises, equipment, knowledge, experience and competent personnel to satisfactorily carry out the work ordered by the contract giver. Contract manufacture may be undertaken only by a manufacturer who holds a valid manufacturing authorization.
- 7.11 The contract acceptor should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements. Arrangements made between the contract acceptor and any third party should ensure that information and knowledge, including that from assessments of the suitability of the third party, are made available in the same way as between the original contract giver and contract acceptor.
- 7.12 The contract acceptor should refrain from any activity (including unauthorized changes outside the terms of the contract) that may adversely affect the quality of the product manufactured and/or analysed for the contract giver.

The contract

- 7.13 There must be a written contract between the contract giver and the contract acceptor which clearly establishes the responsibilities of each party, covering the outsourced activities, the products or operations to which they are related, communication processes relating to the outsourced activities and any technical arrangements made in connection with it.
- 7.14 The contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility and ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.
- 7.15 Technical aspects of the contract should be drawn up by competent persons with suitable knowledge of pharmaceutical technology, analysis and GMP.
- 7.16 All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

- 7.17 The contract should clearly describe who is responsible for contracted activities, e.g. knowledge management, technology transfer, supply chain, subcontracting, testing and releasing materials and undertaking production and QC, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the contract acceptor should take samples at the premises of the manufacturer.
- 7.18 Manufacturing, analytical and distribution records, and reference samples, should be kept by, or be available to, the contract giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect, or to investigating in the case of a suspected falsified product or laboratory fraud, must be accessible and specified in the procedures of the contract giver.
- 7.19 The contract should describe the handling of starting materials, intermediate, bulk and finished products, if they are rejected. It should also describe the procedure to be followed if the contract analysis shows that the tested product must be rejected.

8. Self-inspection, quality audits and suppliers' audits and approval

- 8.1 *Principle.* The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and QC. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

Items for self-inspection

- 8.2 Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:
 - (a) personnel;
 - (b) premises including personnel facilities;
 - (c) maintenance of buildings and equipment;

- (d) storage of starting materials and finished products;
- (e) equipment;
- (f) production and in-process controls;
- (g) QC;
- (h) documentation;
- (i) sanitation and hygiene;
- (j) validation and revalidation programmes;
- (k) calibration of instruments or measurement systems;
- (l) recall procedures;
- (m) complaints management;
- (n) labels control;
- (o) results of previous self-inspections and any corrective steps taken.

Self-inspection team

- 8.3 Management should appoint a self-inspection team consisting of experts in their respective fields who are familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of self-inspection

- 8.4 The frequency with which self-inspections are conducted may depend on company requirements but should preferably be at least once a year. The frequency should be stated in the procedure.

Self-inspection report

- 8.5 A report should be made at the completion of a self-inspection. The report should include:

- (a) self-inspection results;
- (b) evaluation and conclusions;
- (c) recommended corrective actions.

Follow-up action

- 8.6 There should be an effective follow-up programme. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality audit

- 8.7 It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (see section 7, "Contract production and analysis").

Suppliers' audits and approval

- 8.8 The person responsible for QC should have responsibility, together with other relevant departments, for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.
- 8.9 Before suppliers are approved and included in the approved suppliers' list or specifications, they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier's ability to conform with GMP standards.

9. Personnel

- 9.1 *Principle.* The establishment and maintenance of a satisfactory system of QA and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

General

- 9.2 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.
- 9.3 Responsible staff should have its specific duties recorded in written descriptions and adequate authority to carry out its responsibilities. Its duties may be delegated to designated deputies with a satisfactory level of qualifications. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP. The manufacturer should have an organization chart.
- 9.4 All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instruction, relevant to

their needs. All personnel should be motivated to support the establishment and maintenance of high quality standards.

- 9.5 Steps should be taken to prevent unauthorized people from entering production, storage and QC areas. Personnel who do not work in these areas should not use them as a passageway.

Key personnel

- 9.6 Key personnel include the heads of production, the head(s) of quality unit(s) and the authorized person. The quality unit(s) typically comprise the quality assurance and quality control functions. In some cases, these could be combined in one department. The authorized person may also be responsible for one or more of these quality unit(s). Normally, key posts should be occupied by full-time personnel. The heads of production and quality unit(s) should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.
- 9.7 Key personnel responsible for supervising the production and quality unit(s) for pharmaceutical products should possess the qualifications of a scientific education and practical experience required by national legislation. Their education should include the study of an appropriate combination of:
- (a) chemistry (analytical or organic) or biochemistry;
 - (b) chemical engineering;
 - (c) microbiology;
 - (d) pharmaceutical sciences and technology;
 - (e) pharmacology and toxicology;
 - (f) physiology;
 - (g) other related sciences.

They should also have adequate practical experience in the manufacture and QA of pharmaceutical products. In order to gain such experience, a preparatory period may be required, during which they should perform their duties under professional guidance. The scientific education and practical experience of experts should be such as to enable them to exercise independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and QC of pharmaceutical products.

- 9.8 The heads of the production and the quality unit(s) generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, depending on national regulations:

- (a) authorization of written procedures and other documents, including amendments;
- (b) monitoring and control of the manufacturing environment;
- (c) plant hygiene;
- (d) process validation and calibration of analytical apparatus;
- (e) training, including the application and principles of QA;
- (f) approval and monitoring of suppliers of materials;
- (g) approval and monitoring of contract manufacturers;
- (h) designation and monitoring of storage conditions for materials and products;
- (i) performance and evaluation of in-process controls;
- (j) retention of records;
- (k) monitoring of compliance with GMP requirements;
- (l) inspection, investigation and taking of samples in order to monitor factors that may affect product quality.

9.9 The head of production generally has the following responsibilities:

- (a) to ensure that products are produced and stored in accordance with the appropriate documentation in order to obtain the required quality;
- (b) to approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation;
- (c) to ensure that the production records are evaluated and signed by a designated person;
- (d) to check the maintenance of the department, premises and equipment;
- (e) to ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available;
- (f) to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

9.10 The head(s) of the quality unit(s) generally have the following responsibilities:

- (a) to approve or reject starting materials, packaging materials, and intermediate, bulk and finished products in relation to their specifications;
- (b) to evaluate batch records;
- (c) to ensure that all necessary testing is carried out;
- (d) to approve sampling instructions, specifications, test methods and other QC procedures;

- (e) to approve and monitor analyses carried out under contract;
- (f) to check the maintenance of the department, premises and equipment;
- (g) to ensure that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are carried out;
- (h) to ensure that the required initial and continuing training of quality unit personnel is carried out and adapted according to need;
- (i) establishment, implementation and maintenance of the quality system;
- (j) supervision of the regular internal audits or self-inspections;
- (k) participation in external audit (vendor audit);
- (l) participation in validation programmes.

Other duties of QC are summarized in sections 17.3 and 17.4.

- 9.11 The authorized person is responsible for compliance with technical or regulatory requirements related to the quality of finished products and the approval of the release of the finished product for sale or supply.
- 9.12 Assessment of finished products should embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack.
- 9.13 No batch of product is to be released for sale or supply prior to certification by the authorized person(s). In certain countries, by law, the batch release is a task of the authorized person from production together with the authorized person from QC.
- 9.14 The authorized person responsible for approving a batch for release should always ensure that the following requirements have been met:
 - (a) the marketing authorization and the manufacturing authorization requirements for the product have been met for the batch concerned;
 - (b) the principles and guidelines of GMP, as laid down in the guidelines published by WHO, have been followed;
 - (c) the principal manufacturing and testing processes have been validated;
 - (d) all the necessary checks and tests have been performed and account taken of the production conditions and manufacturing records;
 - (e) any planned changes or deviations in manufacturing or QC have been notified in accordance with a well-defined reporting system before any product is released. Such changes may need notification to, and approval by, the medicines regulatory authority;

- (f) any additional sampling, inspection, tests and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations;
 - (g) all necessary production and QC documentation has been completed and endorsed by supervisors trained in appropriate disciplines;
 - (h) appropriate audits, self-inspections and spot-checks are carried out by experienced and trained staff;
 - (i) approval has been given by the head of QC;
 - (j) all relevant factors have been considered, including any not specifically associated with the output batch directly under review (e.g. subdivision of output batches from a common input, factors associated with continuous production runs).
- 9.15 The function of the approval of the release of a finished batch or a product can be delegated to a designated person with appropriate qualifications and experience who will release the product in accordance with an approved procedure. This is normally done by QA by means of batch review.

10. Training

- 10.1 The manufacturer should provide training in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel as required.
- 10.2 Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness periodically assessed. Approved training programmes should be available. Training records should be kept.
- 10.3 Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training.
- 10.4 The concept of QA and all the measures which aid its understanding and implementation should be fully discussed during the training sessions.
- 10.5 Visitors or untrained personnel should preferably not be taken into the production and QC areas. If this is unavoidable, they should be given relevant information in advance (particularly about personal hygiene) and the prescribed protective clothing. They should be closely supervised.

- 10.6 Consultant and contract staff should be qualified for the services they provide. Evidence of this should be included in the training records.

11. Personal hygiene

- 11.1 All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.
- 11.2 All personnel should be trained in the practices of personal hygiene. A high level of personal hygiene should be observed by all those concerned with manufacturing processes. In particular, personnel should be instructed to wash their hands before entering production areas. Signs to this effect should be posted and instructions complied with.
- 11.3 Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials or medicines until the condition is no longer judged to be a risk.
- 11.4 All employees should be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment or personnel) that they consider may adversely affect the products.
- 11.5 Direct contact should be avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product.
- 11.6 To ensure protection of the product from contamination, personnel should wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. Used clothes, if reusable, should be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.
- 11.7 Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines should not be permitted in production, laboratory and storage areas, or in any other areas where they might adversely influence product quality.
- 11.8 Personal hygiene procedures, including the wearing of protective clothing, should apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees, e.g. contractors' employees, visitors, senior managers and inspectors.

12. Premises

12.1 *Principle.* Premises must be located, designed, constructed, adapted and maintained to suit the operations to be carried out.

General

- 12.2 The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and in general, any adverse effect on the quality of products.
- 12.3 Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, or packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning.
- 12.4 Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.
- 12.5 Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.
- 12.6 Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products.
- 12.7 Premises should be cleaned and, where applicable, disinfected according to detailed written procedures. Records should be maintained.
- 12.8 Electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.
- 12.9 Premises should be designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals. There should be a procedure for rodent and pest control.
- 12.10 Premises should be designed to ensure the logical flow of materials and personnel.

Ancillary areas

- 12.11 Rest and refreshment rooms should be separate from manufacturing and control areas.

- 12.12 Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not communicate directly with production or storage areas.
- 12.13 Maintenance workshops should if possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.
- 12.14 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

Storage areas

- 12.15 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.
- 12.16 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean, dry, sufficiently lit and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, controlled, monitored and recorded where appropriate.
- 12.17 Receiving and dispatch bays should be separated and should protect materials and products from the weather. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned, if necessary, before storage.
- 12.18 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.
- 12.19 Segregation should be provided for the storage of rejected, recalled, or returned materials or products.
- 12.20 Highly active and radioactive materials, narcotics, other dangerous medicines, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.
- 12.21 Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labelling and special attention should be paid to sampling and the safe and secure storage of these materials.

- 12.22 There should normally be a separate sampling area for starting materials. (If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.)

Weighing areas

- 12.23 The weighing of starting materials and the estimation of yield by weighing should be carried out in separate weighing areas designed for that use, for example, with provisions for dust control. Such areas may be part of either storage or production areas.

Production areas

- 12.24 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g. penicillins) or biological preparations (e.g. live microorganisms). The production of certain other highly active products, such as some antibiotics, hormones, cytotoxic substances and certain non-pharmaceutical products, should not be conducted in the same facilities. In exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations (including cleaning validation) are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of pharmaceutical products.
- 12.25 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
- 12.26 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.
- 12.27 Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth and free from cracks and open joints, should not shed particulate matter, and should permit easy and effective cleaning and, if necessary, disinfection.
- 12.28 Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses that are difficult to clean. As far as

possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

- 12.29 Drains should be of adequate size and designed and equipped to prevent back-flow. Open channels should be avoided where possible, but if they are necessary they should be shallow to facilitate cleaning and disinfection.
- 12.30 Production areas should be effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity) appropriate to the products handled, to the operations undertaken and to the external environment. These areas should be regularly monitored during both production and non-production periods to ensure compliance with their design specifications.
- 12.31 Premises for the packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix ups, contamination or cross-contamination.
- 12.32 Production areas should be well lit, particularly where visual online controls are carried out.

Quality control areas

- 12.33 QC laboratories should be separated from production areas. Areas where biological, microbiological or radioisotope test methods are employed should be separated from each other.
- 12.34 QC laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix ups and cross-contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), solvents, reagents and records.
- 12.35 The design of the laboratories should take into account the suitability of construction materials, prevention of fumes, and ventilation. There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions are needed for biological, microbiological and radioisotope laboratories.
- 12.36 A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors, or where it is necessary to isolate the instruments.

13. Equipment

- 13.1 Equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.
- 13.2 Equipment should be installed in such a way as to minimize any risk of error or of contamination.
- 13.3 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.
- 13.4 All service pipework and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.
- 13.5 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated according to a fixed schedule.
- 13.6 Production equipment should be thoroughly cleaned according to a fixed schedule.
- 13.7 Laboratory equipment and instruments should be suited to the testing procedures undertaken.
- 13.8 Washing, cleaning and drying equipment should be chosen and used so as not to be a source of contamination.
- 13.9 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to an extent that would affect the quality of the product.
- 13.10 Defective equipment should be removed from production and QC areas. If this is not possible, it should be clearly labelled as defective to prevent use.
- 13.11 Closed equipment should be used whenever appropriate. Where open equipment is used or equipment is opened, precautions should be taken to minimize contamination.
- 13.12 Non-dedicated equipment should be cleaned according to validated cleaning procedures between being used for production of different pharmaceutical products to prevent cross-contamination.

- 13.13 Current drawings of critical equipment and support systems should be maintained.

14. Materials

- 14.1 *Principle.* The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (starting and packaging).
- 14.2 Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labelling materials.

General

- 14.3 No materials used for operations such as cleaning, lubrication of equipment and pest control should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g. food grade) to minimize health risks.
- 14.4 All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.
- 14.5 All materials and products should be stored under the appropriate conditions established by the manufacturer, and in an orderly fashion, to permit batch segregation and stock rotation by a first-expire, first-out rule.
- 14.6 Water used in the manufacture of pharmaceutical products should be suitable for its intended use.

Starting materials

- 14.7 The purchase of starting materials is an important operation that should involve staff who have a particular and thorough knowledge of the products and suppliers.
- 14.8 Starting materials should be purchased only from approved suppliers and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is beneficial for all critical aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements as well as complaints and rejection procedures, to be contractually agreed between the manufacturer and the supplier.
- 14.9 For each consignment, at a minimum, the containers should be checked at least for integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.

- 14.10 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled, if required, with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.
- 14.11 Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the QC department and investigated.
- 14.12 If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release.
- 14.13 Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:
 - (a) the designated name of the product and the internal code reference where applicable;
 - (b) the batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;
 - (c) the status of the contents (e.g. in quarantine, on test, released, rejected, returned, recalled);
 - (d) where appropriate, an expiry date or a date beyond which retesting is necessary. When fully validated computerized storage systems are used, not all of the above information need be in a legible form on the label.
- 14.14 There should be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.
- 14.15 Only starting materials released by the QC department and within their shelf-life should be used.
- 14.16 Starting materials should be dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.
- 14.17 Each dispensed material and its weight or volume should be independently checked and the check recorded.
- 14.18 Materials dispensed for each batch of the final product should be kept together and conspicuously labelled as such.

Packaging materials

- 14.19 The purchase, handling and control of primary and printed packaging materials should be as for starting materials.
- 14.20 Particular attention should be paid to printed packaging materials. They should be stored in secure conditions so as to exclude the possibility of unauthorized access. Roll feed labels should be used wherever possible. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix ups. Packaging materials should be issued for use only by designated personnel following an approved and documented procedure.
- 14.21 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.
- 14.22 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and its disposal recorded.
- 14.23 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.

Intermediate and bulk products

- 14.24 Intermediate and bulk products should be kept under appropriate conditions.
- 14.25 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

Finished products

- 14.26 Finished products should be held in quarantine until their final release, after which they should be stored as usable stock under conditions established by the manufacturer.
- 14.27 The evaluation of finished products and the documentation necessary for release of a product for sale are described in section 17, “Good practices in quality control”.

Rejected, recovered, reprocessed and reworked materials

- 14.28 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed in a timely manner. Whatever action is taken should be approved by authorized personnel and recorded.

- 14.29 The reworking or recovery of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record should be kept of the reworking or recovery. A reworked batch should be given a new batch number.
- 14.30 The introduction of all or part of earlier batches, conforming to the required quality standards, into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life. The recovery should be recorded.
- 14.31 The need for additional testing of any finished product that has been reprocessed, reworked or into which a recovered product has been incorporated, should be considered by the QC department.

Recalled products

- 14.32 Recalled products should be identified and stored separately in a secure area until a decision is taken on their fate. This decision should be made as soon as possible.

Returned goods

- 14.33 Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabelling, or alternative action taken only after they have been critically assessed by the QC function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.

Reagents and culture media

- 14.34 There should be records for the receipt and preparation of reagents and culture media.
- 14.35 Reagents made up in the laboratory should be prepared according to written procedures and appropriately labelled. The label should indicate the concentration, standardization factor, shelf-life, the date when re-standardization is due, and the storage conditions. The label should be signed and dated by the person preparing the reagent.

14.36 Both positive and negative controls should be applied to verify the suitability of culture media each time they are prepared and used. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

Reference standards

14.37 Whenever official reference standards exist, these should preferably be used.

14.38 Official reference standards should be used only for the purpose described in the appropriate monograph.

14.39 Reference standards prepared by the producer should be tested, released and stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.

14.40 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization.

14.41 Reference standards should be properly labelled with at least the following information:

- (a) name of the material;
- (b) batch or lot number and control number;
- (c) date of preparation;
- (d) shelf-life;
- (e) potency;
- (f) storage conditions.

14.42 All in-house reference standards should be standardized against an official reference standard, when available, initially and at regular intervals thereafter.

14.43 All reference standards should be stored and used in a manner that will not adversely affect their quality.

Waste materials

14.44 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

14.45 Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

Miscellaneous

- 14.46 Rodenticides, insecticides, fumigating agents and sanitizing materials should not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials or finished products.

15. Documentation

- 15.1 *Principle.* Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a medicine for sale; to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases some or all of the documents described below may be brought together, but they will usually be separate.

General

- 15.2 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.
- 15.3 Documents should be approved, signed and dated by the appropriate responsible persons. No document should be changed without authorization and approval.
- 15.4 Documents should have unambiguous contents: the title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.
- 15.5 Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specific period of time.
- 15.6 Where documents require the entry of data, these entries should be clear, legible and indelible. Sufficient space should be provided for such entries.

- 15.7 Any alteration made to a document should be signed and dated; the alteration should be done in such a way as to permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.
- 15.8 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records should be retained for at least one year after the expiry date of the finished product.
- 15.9 Data (and records for storage) may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed SOPs relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer system, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked. Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, electronic discs, paper printouts or other means. It is particularly important that, during the period of retention, the data are readily available.

Documents required

Labels

- 15.10 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (e.g. quarantined, accepted, rejected, clean).
- 15.11 All finished medicines should be identified by labelling, as required by the national legislation, bearing at least the following information:
 - (a) the name of the medicines;
 - (b) a list of the active ingredients (if applicable, with the INN), showing the amount of each present and a statement of the net contents (e.g. number of dosage units, weight, volume);
 - (c) the batch number assigned by the manufacturer;
 - (d) the expiry date in an uncoded form;
 - (e) any special storage conditions or handling precautions that may be necessary;
 - (f) directions for use, and warnings and precautions that may be necessary;

- (g) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.
- 15.12 For reference standards, the label and/or accompanying document should indicate potency or concentration, date of manufacture, expiry date, date the closure is first opened, storage conditions and control number, as appropriate.

Specifications and testing procedures

- 15.13 Testing procedures described in documents should be validated in the context of available facilities and equipment before they are adopted for routine testing.
- 15.14 There should be appropriately authorized and dated specifications, including tests on identity, content, purity and quality, for starting and packaging materials and for finished products; where appropriate, they should also be available for intermediate or bulk products. Specifications for water, solvents and reagents (e.g. acids and bases) used in production should be included.
- 15.15 Each specification should be approved, signed and dated, and maintained by the QC or QA units. Specifications for starting materials, intermediates, bulk, finished products and packaging materials are referred to in sections 15.18–15.21.
- 15.16 Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.
- 15.17 Pharmacopoeias, reference standards, reference spectra and other reference materials should be available in the QC laboratory.

Specifications for starting and packaging materials

- 15.18 Specifications for starting, primary and printed packaging materials should provide, if applicable, a description of the materials, including:
- the designated name (if applicable, the INN) and internal code reference;
 - the reference, if any, to a pharmacopoeial monograph;
 - qualitative and quantitative requirements with acceptance limits.

Depending on the company's practice other data may be added to the specification, such as:

- the supplier and the original producer of the materials;
- a specimen of printed materials;
- directions for sampling and testing, or a reference to procedures;
- storage conditions and precautions;
- the maximum period of storage before reexamination.

Packaging material should conform to specifications, and should be compatible with the material and/or with the medicines it contains. The material should be examined for compliance with the specification, and for defects as well as for the correctness of identity markings.

- 15.19 Documents describing testing procedures should state the required frequency for re-assaying each starting material, as determined by its stability.

Specifications for intermediate and bulk products

- 15.20 Specifications for intermediate and bulk products should be available. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

- 15.21 Specifications for finished products should include:

- (a) the designated name of the product and the code reference, where applicable;
- (b) the designated name(s) of the active ingredient(s) (if applicable, with the INN(s));
- (c) the formula or a reference to the formula;
- (d) a description of the dosage form and package details;
- (e) directions for sampling and testing or a reference to procedures;
- (f) the qualitative and quantitative requirements, with acceptance limits;
- (g) the storage conditions and precautions, where applicable;
- (h) the shelf-life.

Master formulae

- 15.22 A formally authorized master formula should exist for each product and batch size to be manufactured.

- 15.23 The master formula should include:

- (a) the name of the product, with a product reference code relating to its specification;
- (b) a description of the dosage form, strength of the product and batch size;
- (c) a list of all starting materials to be used (if applicable with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);

- (d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
- (e) a statement of the processing location and the principal equipment to be used;
- (f) the methods, or reference to the methods, to be used for preparing and operating the critical equipment, e.g. cleaning (especially after a change in product), assembling, calibrating, sterilizing, use;
- (g) detailed step-wise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
- (h) the instructions for any in-process controls with their limits;
- (i) where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions;
- (j) any special precautions to be observed.

Packaging instructions

15.24 Formally authorized packaging instructions should exist for each product, pack size and type. These should normally include, or make reference to:

- (a) the name of the product;
- (b) a description of its pharmaceutical form, strength and, where applicable, method of application;
- (c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
- (d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications for each packaging material;
- (e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;
- (f) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations;
- (g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- (h) details of in-process controls with instructions for sampling and acceptance limits.

Batch processing records

- 15.25 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programs are recommended. Transcribing from approved documents should be avoided.)
- 15.26 Before any processing begins a check should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.
- 15.27 During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations:
- (a) the name of the product;
 - (b) the number of the batch being manufactured;
 - (c) dates and times of commencement, of significant intermediate stages, and of completion of production;
 - (d) the name of the person responsible for each stage of production;
 - (e) the initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g. weighing);
 - (f) the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
 - (g) any relevant processing operation or event and the major equipment used;
 - (h) the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
 - (i) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;
 - (j) notes on special problems including details, with signed authorization for any deviation from the master formula.

Batch packaging records

- 15.28 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the approved packaging instructions,

and the method of preparing such records should be designed to avoid errors. (Copying or validated computer programs are recommended. Transcribing from approved documents should be avoided.)

- 15.29 Before any packaging operation begins, checks should be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded.
- 15.30 The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:
- (a) the name of the product, the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;
 - (b) the date(s) and time(s) of the packaging operations;
 - (c) the name of the responsible person carrying out the packaging operation;
 - (d) the initials of the operators of the different significant steps;
 - (e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
 - (f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product if it is unpacked or a record of returning product that has not been packaged to the storage area;
 - (g) whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;
 - (h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
 - (i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

Standard operating procedures and records

15.31 SOPs and associated records of actions taken or, where appropriate, conclusions reached should be available for:

- (a) equipment assembly and validation;
- (b) analytical apparatus and calibration;
- (c) maintenance, cleaning and sanitization;
- (d) personnel matters including qualification, training, clothing and hygiene;
- (e) environmental monitoring;
- (f) pest control;
- (g) complaints;
- (h) recalls;
- (i) returns.

15.32 There should be SOPs and records for the receipt of each delivery of starting material and primary and printed packaging material.

15.33 The records of the receipts should include:

- (a) the name of the material on the delivery note and the containers;
- (b) the “in-house” name and/or code of material if different from (a);
- (c) the date of receipt;
- (d) the supplier’s name and, if possible, manufacturer’s name;
- (e) the manufacturer’s batch or reference number;
- (f) the total quantity, and number of containers received;
- (g) the batch number assigned after receipt;
- (h) any relevant comment (e.g. state of the containers).

15.34 There should be SOPs for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

15.35 SOPs should be available for each instrument and piece of equipment (e.g. use, calibration, cleaning, maintenance) and placed in close proximity to the equipment.

15.36 There should be SOPs for sampling, which specify the person(s) authorized to take samples.

15.37 The sampling instructions should include:

- (a) the method of sampling and the sampling plan;

- (b) the equipment to be used;
 - (c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
 - (d) the amount(s) of sample(s) to be taken;
 - (e) instructions for any required subdivision of the sample;
 - (f) the type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling, and labelling;
 - (g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.
- 15.38 There should be an SOP describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.
- 15.39 The SOPs for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.
- 15.40 The SOP for batch numbering should ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.
- 15.41 Batch-number allocation should be immediately recorded, e.g. in a logbook. The record should include at least the date of allocation, product identity and size of batch.
- 15.42 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.
- 15.43 Analysis records should include at least the following data:
- (a) the name of the material or product and, where applicable, dosage form;
 - (b) the batch number and, where appropriate, the manufacturer and/or supplier;
 - (c) references to the relevant specifications and testing procedures;
 - (d) test results, including observations and calculations, and reference to any specifications (limits);
 - (e) date(s) and reference number(s) of testing;
 - (f) the initials of the persons who performed the testing;
 - (g) the date and initials of the persons who verified the testing and the calculations, where appropriate;
 - (h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

- 15.44 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.
- 15.45 Records should be maintained of the distribution of each batch of a product in order, for example, to facilitate the recall of the batch if necessary.
- 15.46 Records should be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning or repair operations, including dates and the identity of the people who carried out these operations.
- 15.47 The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.
- 15.48 There should be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities and equipment to be cleaned. Such written procedures should be followed.

16. Good practices in production

- 16.1 *Principle.* Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

General

- 16.2 All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.
- 16.3 Deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be in accordance with an approved procedure. The authorization of the deviation should be approved in writing by a designated person, with the involvement of the QC department, when appropriate.
- 16.4 Checks on yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
- 16.5 Operations on different products should not be carried out simultaneously or consecutively in the same room or area unless there is no risk of mix up or cross-contamination.

- 16.6 At all times during processing, all materials, bulk containers, major items of equipment, and, where appropriate, the rooms and packaging lines being used, should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and the batch number. Where applicable, this indication should also mention the stage of production. In some cases it may be useful to also record the name of the previous product that has been processed.
- 16.7 Access to production premises should be restricted to authorized personnel.
- 16.8 Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.
- 16.9 In-process controls are usually performed within the production area. The performance of such in-process controls should not have any negative effect on the quality of the product or another product (e.g. cross-contamination or mix up).

Prevention of cross-contamination and bacterial contamination during production

- 16.10 When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g. supply and extraction of air of suitable quality).
- 16.11 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, particles, vapours, sprays or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, certain hormones, cytotoxic substances, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time.
- 16.12 Cross-contamination should be avoided by taking appropriate technical or organizational measures, for example:
 - (a) carrying out production in dedicated and self-contained areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations and certain other biologicals);

- (b) conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;
- (c) providing appropriately designed airlocks, pressure differentials, and air supply and extraction systems;
- (d) minimizing the risk of contamination caused by recirculation or reentry of untreated or insufficiently treated air;
- (e) wearing protective clothing where products or materials are handled;
- (f) using cleaning and decontamination procedures of known effectiveness;
- (g) using a “closed system” in production;
- (h) testing for residues;
- (i) using cleanliness status labels on equipment.

16.13 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to SOPs.

16.14 Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g. for microbiological and particulate matter, where appropriate).

Processing operations

16.15 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels or documents not required for the current operation.

16.16 Any necessary in-process controls and environmental controls should be carried out and recorded.

16.17 Means should be instituted of indicating failures of equipment or of services (e.g. water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. After use, production equipment should be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.

16.18 Time limits for storage of equipment after cleaning and before use should be stated and based on relevant data.

16.19 Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

- 16.20 Any significant deviation from the expected yield should be recorded and investigated.
- 16.21 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in the correct manner.
- 16.22 Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes should be sanitized and stored according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.
- 16.23 Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument.
- 16.24 Repair and maintenance operations should not present any hazard to the quality of the products.

Packaging operations

- 16.25 When the programme for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or an alternative system that will provide equal assurance.
- 16.26 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents used previously and which are not required for the current operation. The line clearance should be performed according to an appropriate procedure and checklist, and recorded.
- 16.27 The name and batch number of the product being handled should be displayed at each packaging station or line.
- 16.28 Normally, filling and sealing should be followed as quickly as possible by labelling. If labelling is delayed, appropriate procedures should be applied to ensure that no mix ups or mislabelling can occur.
- 16.29 The correct performance of any printing (e.g. of code numbers or expiry dates) done separately or in the course of the packaging should be checked and recorded.

Attention should be paid to printing by hand, which should be rechecked at regular intervals.

- 16.30 Special care should be taken when cut labels are used and when overprinting is carried out off-line, and in hand-packaging operations. Roll-feed labels are normally preferable to cut labels in helping to avoid mix ups. Online verification of all labels by automated electronic means can be helpful in preventing mix ups, but checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly. When labels are attached manually, in-process control checks should be performed more frequently.
- 16.31 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.
- 16.32 Regular online control of the product during packaging should include at a minimum checks on:
 - (a) the general appearance of the packages;
 - (b) whether the packages are complete;
 - (c) whether the correct products and packaging materials are used;
 - (d) whether any overprinting is correct;
 - (e) the correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

- 16.33 Products that have been involved in an unusual event during packaging should be reintroduced into the process only after special inspection, investigation and approval by authorized personnel. A detailed record should be kept of this operation.
- 16.34 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated, satisfactorily accounted for, and recorded before release.
- 16.35 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure requiring checks to be performed before returning unused materials should be followed if uncoded printed materials are returned to stock.
- 16.36 Production records should be reviewed as part of the approval process of batch release before transfer to the authorized person. Any divergence or failure of a batch to meet production specifications should be thoroughly investigated. The

investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

17. Good practices in quality control

- 17.1 QC is the part of GMP concerned with sampling, specifications and testing, and with the organization and documentation which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be compliant with the requirements. QC is not confined to laboratory operations, but may be involved in many decisions concerning the quality of the product.
- 17.2 The independence of QC from production is considered fundamental.
- 17.3 Each manufacturer should have a QC function. The QC function should be independent of other departments and under the authority of a person with appropriate qualifications and experience. Adequate resources must be available to ensure that all the QC arrangements are effectively and reliably carried out. The basic requirements for QC are as follows:
- (a) adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
 - (b) samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved by the QC department;
 - (c) qualification and validation;
 - (d) records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated;
 - (e) the finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container and correctly labelled;
 - (f) records must be made of the results of inspecting and testing the materials and intermediate, bulk and finished products against specifications; product

assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;

- (g) sufficient samples of starting materials and products must be retained to permit future examination of the product if necessary; the retained product must be kept for the appropriate time in its final pack unless the pack is exceptionally large, in which case one that is equivalent to the marketed packaging system may be used.

17.4 Other QC responsibilities include:

- (a) establishing, validating and implementing all QC procedures;
- (b) evaluating, maintaining and storing reference standards for substances;
- (c) ensuring the correct labelling of containers of materials and products;
- (d) ensuring that the stability of the active pharmaceutical ingredients and products is monitored;
- (e) participating in the investigation of complaints related to the quality of the product;
- (f) participating in environmental monitoring;
- (g) participation in QRM programmes.

These activities should be carried out in accordance with written procedures and, where necessary, recorded.

17.5 QC personnel must have access to production areas for sampling and investigation as appropriate.

Control of starting materials and intermediate, bulk and finished products

17.6 All tests should follow the instructions given in the relevant written test procedure for each material or product. The result should be checked by the supervisor before the material or product is released or rejected.

17.7 Samples should be representative of the batches of material from which they are taken in accordance with the approved written procedure.

17.8 Sampling should be carried out so as to avoid contamination or other adverse effects on quality. The containers that have been sampled should be marked accordingly and carefully resealed after sampling.

17.9 Care should be taken during sampling to guard against contamination or mix up of, or by, the material being sampled. All sampling equipment that comes into

contact with the material should be clean. Some particularly hazardous or potent materials may require special precautions.

17.10 Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.

17.11 Each sample container should bear a label indicating:

- (a) the name of the sampled material;
- (b) the batch or lot number;
- (c) the number of the container from which the sample has been taken;
- (d) the number of the sample;
- (e) the signature of the person who has taken the sample;
- (f) the date of sampling.

17.12 Out-of-specification results obtained during testing of materials or products should be investigated in accordance with an approved procedure. Records should be maintained.

Test requirements

Starting and packaging materials

17.13 Before releasing a starting or packaging material for use, the QC manager should ensure that the materials have been tested for conformity with specifications for identity, strength, purity and other quality parameters.

17.14 An identity test should be conducted on a sample from each container of starting material (see also section 14.14). It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labelled. This validation should take account of at least the following aspects:

- the nature and status of the manufacturer and of the supplier and their understanding of the GMP requirements;
- the QA system of the manufacturer of the starting material;
- the manufacturing conditions under which the starting material is produced and controlled;
- the nature of the starting material and the medicinal products in which it will be used.

Under such a system it is possible that a validated procedure for exemption from the requirement for identity testing of each incoming container of starting material could be accepted for the following:

- starting materials coming from a single product manufacturer or plant; or
- starting materials coming directly from a manufacturer, or in the manufacturer's sealed container where there is a history of reliability, and regular audits of the manufacturer's QA system are conducted by the purchaser (the manufacturer of the medicinal product) or by an officially accredited body.

It is improbable that such a procedure could be satisfactorily validated for either:

- starting materials supplied by intermediaries, such as brokers, where the source of manufacture is unknown or not audited; or
- starting materials for use in parenteral products.

17.15 Each batch (lot) of printed packaging materials must be examined following receipt.

17.16 In lieu of full testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results (see sections 8.8 and 8.9) and through on-site audits of the supplier's capabilities. (This does not affect section 17.15.) Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain at least the following information (7):

- (a) identification (name and address) of the issuing supplier;
- (b) signature of the competent official, and statement of his or her qualifications;
- (c) the name of the material tested;
- (d) the batch number of the material tested;
- (e) the specifications and methods used;
- (f) the test results obtained;
- (g) the date of testing.

In-process control

17.17 In-process control records should be maintained and form a part of the batch records (see section 15.25).

Finished products

17.18 For each batch of medicines, there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

- 17.19 Products failing to meet the established specifications or any other relevant quality criteria should be rejected.

Batch record review

- 17.20 QC records should be reviewed as part of the approval process of batch release before transfer to the authorized person. Any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.
- 17.21 Retention samples from each batch of finished product should be kept for at least one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials should be retained for at least one year beyond the expiry date of the corresponding finished product. Other starting materials (other than solvents, gases and water) should be retained for a minimum of two years if their stability allows. Retention samples of materials and products should be of a size sufficient to permit at least two full reexaminations.

Stability studies

- 17.22 QC should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.
- 17.23 QC should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.
- 17.24 A written programme for ongoing stability determination should be developed and implemented to include elements such as:
- (a) a complete description of the medicine involved in the study;
 - (b) the complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
 - (c) provision for the inclusion of a sufficient number of batches;
 - (d) the testing schedule for each medicine;
 - (e) provision for special storage conditions;
 - (f) provision for adequate sample retention;

- (g) a summary of all the data generated, including the evaluation and the conclusions of the study.
- 17.25 Stability should be determined prior to marketing and following any significant changes, for example, in processes, equipment or packaging materials.

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1.2 WHO good manufacturing practices: guidelines on validation

Annex 3, WHO Technical Report Series, 1019,
2019

Background

The need for revision of the published World Health Organization (WHO) *Supplementary guidelines on good manufacturing practices: validation* (1) was identified by the Prequalification of Medicines Programme and a first draft document was circulated for comment in early 2013. The focus, at that time, was revision of the appendix on *Non-sterile process validation* (Appendix 7) (2), which had been revised and was adopted by the ECSPP at its Forty-ninth meeting in October 2014 (3).

The overarching text presented in this annex constitutes the general principles of the new guidance on validation.

The following appendices included in this annex address specific aspects of validation and are intended to complement the general text on validation:

- Appendix 1. Validation of heating, ventilation and air-conditioning systems (as cross-reference to TRS 1010, Annex 8 (4))
- Appendix 2. Validation of water systems for pharmaceutical use (as published in TRS 937, Annex 4, 2006 and as cross-reference to TRS 970, Annex 2, 2012 (5))
- Appendix 3. Cleaning validation (as published in TRS and TRS 937, Annex 4, 2006 and as cross-reference to TRS 970, Annex 2, 2012 (5))
- Appendix 4. Analytical procedure validation (adopted, subject to a review of the comments received by a subgroup of the Expert Committee)
- Appendix 5. Validation of computerized systems (adopted, subject to the changes discussed by the Expert Committee)
- Appendix 6. Guidelines on qualification (adopted, subject to a review of the comments received by a subgroup of the Expert Committee)
- Appendix 7. Non-sterile process validation (as published in TRS 992, Annex 3, 2015 (3)).

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1. Introduction

- 1.1 Validation is an essential part of good practices, including good manufacturing practices (GMP) (6) and good clinical practices (GCP). It is therefore an element of the pharmaceutical quality system. Validation, as a concept, incorporates qualification and should be applied over the life-cycle of, for example, a product, process, method, system, equipment or utility.
- 1.2 These guidelines cover the general principles of qualification and validation. In addition to the main text, appendices on some validation and qualification activities (such as applied to heating, ventilation and air-conditioning systems, water systems, cleaning, analytical methods, computerized systems, and non-sterile processes) are included.
- 1.3 The following principles apply:
 1. the execution of qualification and validation should be in compliance with regulatory expectations (7);
 2. quality must be designed and built into the product;
 3. quality cannot be inspected or tested into the product;
 4. principles of quality risk management (8) should be applied in determining the need, scope and extent of qualification and validation;
 5. ongoing review should take place, to ensure that the qualified or validated state is maintained and opportunities for continuing improvement are identified.
- 1.4 Provision should be made for appropriate resources such as personnel, financing and time to organize, plan and execute qualification and validation.

2. Scope

- 2.1 These guidelines focus mainly on the overall concept of qualification and validation and are not intended to be prescriptive in specific validation requirements. This document serves as general guidance only and the principles may be considered useful in its application in the production and control of starting materials and finished pharmaceutical products, as well as other areas such as GCP. Although the principles addressed in this guideline are applicable, qualification and validation of specific products, methods, processes and systems, such as bioanalytical methods, and manufacturing processes for sterile products, may require other considerations and a detailed approach that is beyond the scope of this document.

- 2.2 There are many factors affecting the different types of validation and it is, therefore, not intended to define and address all aspects related to one particular type of validation here.
- 2.3 The general text in the main part of these guidelines may be applicable to qualification and validation of premises, equipment, utilities, systems, methods, processes and procedures.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

calibration. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

change control/change management. A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure the system is maintained in a validated state.

cleaning validation. Documented evidence to establish that cleaning procedures are removing residues to predetermined levels of acceptability, taking into consideration factors such as batch size, dosing, toxicology and equipment size.

computerized system validation. Confirmation by examination and provision of objective documented evidence that specifications for computerized systems conform to user needs and intended uses, and that all requirements can be consistently fulfilled.

concurrent validation. Validation carried out during routine production of products intended for sale.

design qualification. Documented verification that the proposed design of facilities, systems and equipment is suitable for the intended purpose.

installation qualification. Documented verification that the installations (such as machines equipment and instruments, computer system components, measuring devices, utilities and manufacturing) used in a processor system are appropriately selected and correctly installed, in accordance with established specifications.

operational qualification. Documented verification that the system or subsystem operates as intended over all anticipated operating ranges.

performance qualification. Documented verification that the equipment or system performs consistently and reproducibly within defined specifications and parameters in its normal operating environment (i.e. in the production environment).

process validation. The collection and evaluation of data, throughout the product life-cycle, which provides documented scientific evidence that a process is capable of consistently delivering quality products.

prospective validation. Validation carried out during the development stage, on the basis of a risk analysis of the production process, which is broken down into individual steps; these are then evaluated on the basis of past experience, to determine whether they may lead to critical situations.

qualification. Documented evidence that premises, systems or equipment are able to achieve the predetermined specifications when properly installed, and/or work correctly and lead to the expected results.

revalidation. Repeated validation of a previously validated system (or a part thereof), to ensure continued compliance with established requirements.

standard operating procedure. An authorized written procedure giving instructions for performing operations that are not necessarily specific to a given product or material but of a more general nature (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain standard operating procedures may be used to supplement product-specific master-batch production documentation.

validation. Action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.

validation master plan. A high-level document that summarizes the manufacturer's overall philosophy and approach, to be used for establishing performance adequacy. It provides information on the manufacturer's qualification and validation work programme and defines details of and timelines for the work to be performed, including a statement of the responsibilities of those implementing the plan.

validation protocol. A document describing the activities to be performed during validation, including the acceptance criteria.

validation report. A document in which the records, results and evaluation of validation are documented and summarized. It should also contain a conclusion of the outcome of the validation.

verification. The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with established requirements and specifications.

worst case. A condition or set of conditions encompassing the upper and lower processing limits for operating parameters and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily include product or process failure.

4. Relationship between validation and qualification

- 4.1 In general, qualification and validation follow similar underlying principles. The term “qualification” is normally used, for example, for equipment and utilities, and “validation”, for example, for systems, methods and processes.
- 4.2 Qualification normally precedes validation.

5. Validation

Approaches to qualification and validation

- 5.1 Manufacturers should organize and plan qualification and validation in a manner that will ensure product quality, safety and efficacy throughout its life-cycle.
- 5.2 Statistical evaluation should be applied, where appropriate, and provide scientific evidence that, for example, the process, system or other related aspect is appropriately qualified or validated.
- 5.3 Qualification and validation should be done in accordance with predetermined protocols, and the results appropriately documented, in reports.
- 5.4 There should be an appropriate and effective quality management system supporting the organization, planning, execution and management of qualification and validation.
- 5.5 Senior management should ensure that there are sufficient resources to perform validation in a timely manner. Management and persons responsible for quality assurance should be actively involved in the process and authorization of protocols and reports.
- 5.6 Personnel with appropriate education and experience should be responsible for qualification and validation.
- 5.7 There should be a specific programme or schedule to support planning and execution of qualification and validation activities.
- 5.8 Qualification and validation should be performed in a structured way, according to the documented protocols and procedures.
- 5.9 Qualification and validation (as appropriate), should be performed:
 - for new premises, equipment and utilities;
 - for new systems, methods, processes and procedures;
 - when changes are made, depending on the outcome of risk assessment;

- where necessary or indicated, based on the outcome of periodic review (and may include requalification and revalidation).
- 5.10 The scope and extent of qualification and validation should be based on knowledge, experience and the outcome of principles of quality risk management, as described in the *WHO guidelines on quality risk management* (8).
- 5.11 Where necessary, worst-case situations or specific challenge tests should be considered for inclusion in the qualification and validation.

6. Documentation

6.1 Documents associated with qualification and validation may include:

- validation master plan;
- standard operating procedures (SOPs);
- specifications;
- protocols and reports;
- risk assessment outcomes;
- process flowcharts;
- operator manuals;
- training records;
- calibration procedures and records;
- sampling plans;
- testing plans and methods;
- statistical methods and results;
- history of qualification and validation;
- plan for ensuring maintaining a validated state including review of validation status.

7. Validation master plan

7.1 A manufacturer should have a validation master plan that reflects the key elements of validation. It should be concise and clear and at least contain reference to/have a short description of the following:

- title page and authorization (approval signatures and dates);
- table of contents;
- abbreviations and glossary;
- validation policy;

- philosophy, intention and approach to validation;
- roles and responsibilities of relevant personnel;
- resources to ensure that qualification and validation are done;
- outsourced services (selection, qualification, management through the life-cycle);
- scope of qualification and validation;
- documentation required in qualification and validation, such as procedures, certificates, protocols and reports;
- premises qualification, such as room verification where appropriate;
- qualification of utilities;
- equipment and instrument qualification;
- process validation;
- cleaning validation;
- personnel qualification (such as analyst qualification);
- analytical method validation;
- computerized system validation;
- establishment of acceptance criteria;
- life-cycle management, including retirement policy;
- requalification and revalidation;
- relationship with other quality management elements;
- validation matrix (such as a table indicating the history and status of qualification and validation on-site);
- retention of qualification and validation documentation;
- deviation management;
- change control;
- risk management principles;
- training;
- references.

7.2 The validation master plan should be reviewed at regular intervals and kept up to date, according to current GMP.

8. Qualification and validation protocols

8.1 There should be qualification and validation protocols describing the qualification and validation to be performed.

- 8.2 As a minimum, the protocols should be appropriate for the qualification or validation to be executed, and may include the following significant background information:
- a unique document number and version number;
 - the objective and scope;
 - the site;
 - the responsible personnel;
 - reference to applicable standard operating procedures;
 - equipment or instruments to be used;
 - reference to standards, as appropriate;
 - the stage of validation or qualification;
 - the processes and/or parameters;
 - sampling, testing and monitoring requirements;
 - stress testing, where appropriate;
 - calibration requirements;
 - predetermined acceptance criteria for drawing conclusions;
 - change control, deviations;
 - attachments and reference to attachments, including source data (where relevant);
 - archiving and retention.
- 8.3 There should be a description of the procedure for review, evaluation and interpretation of results, including the application of statistical methods, where appropriate.
- 8.4 The protocol should be approved by responsible persons, including the quality unit, prior to use. Any changes to a protocol should be approved prior to implementation of the change.
- 8.5 The protocol should be executed by trained personnel. Records of the training and assessment should be retained.

9. Qualification and validation reports

- 9.1 There should be written reports on the qualification and validation performed.
- 9.2 Reports should reflect the protocols and procedures followed and include at least the title and objective of the study; reference to the protocol; reference to the appropriate

risk assessment; details of materials, equipment, programmes and cycles used; procedures and test methods; data; changes and deviations; out-of-specification and non-conformance results, with appropriate traceability; and a conclusion.

- 9.3 Results should be recorded and be in compliance with good data and record management practices (7).
- 9.4 Results should be reviewed, analysed and compared against the predetermined acceptance criteria, interpreted and statistically analysed, where appropriate.
- 9.5 Results should meet the acceptance criteria. Out-of-specification and out-of-limit results should be documented and investigated according to appropriate procedures. If these are accepted, this should be justified. Where necessary, further studies should be considered.
- 9.6 The conclusion of the report should state whether or not the outcome of the qualification and/or validation was considered successful, and should make recommendations for future monitoring and setting of alert and action limits, where applicable.
- 9.7 The departments responsible for the qualification and validation work should approve the completed report.
- 9.8 When appropriate, the quality assurance department should approve the report. The criteria for approval should be in accordance with the company's quality assurance system.

10. Qualification

- 10.1 There are different approaches in qualification. The manufacturer should select an appropriate approach for the conduct thereof (see Appendix 6).
- 10.2 All relevant SOPs for operation, maintenance and calibration should be prepared during qualification.
- 10.3 Training should be provided to operators, and training records should be maintained.
- 10.4 Normally, qualification should be completed before process validation is performed.
- 10.5 The process of qualification should be a logical, systematic process and follow a logical flow from the premises, followed by utilities, equipment, to procedures and processes.

- 10.6 Stages of qualification should normally start with the preparation of user requirement specifications (URS). Depending on the function and operation of the utility, equipment or system, this is followed by, as appropriate, different stages in qualification such as design qualification (DQ), a factory acceptance test (FAT), site acceptance test (SAT), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).
- 10.7 One stage of qualification should be successfully completed before the next stage is initiated. For example, OQ normally follows IQ but, depending on the complexity of the equipment, it may be performed as a combined installation/operation qualification (IOQ). Conditional approval to proceed to the next qualification stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity.
- 10.8 In some cases, only IQ and OQ may be required, as the correct operation of the equipment, utility or system could be considered to be a sufficient indicator of its performance.
- 10.9 Major equipment and critical utilities and systems, however, may require URS, DQ, IQ, OQ and PQ.
- 10.10 Computerized systems, including equipment with software component(s), should be appropriately qualified and validated (see Appendices 5 and 6).

User requirement specifications

- 10.11 Manufacturers should prepare a document that describes the requirements for the item (such as system(s) for a utility; or equipment) to be sourced. The requirements may include specifications and should ensure that possible GMP risks are addressed; include technical requirements; and reference associated documentation.
- 10.12 The URS should be used when selecting the required item from an approved supplier, and to verify suitability throughout the subsequent stages of qualification.

Design qualification

- 10.13 DQ should provide documented evidence that the design specifications were met and are in accordance with the URS.

Factory acceptance test and site acceptance test

- 10.14 Where appropriate, FAT and SAT should be performed to verify the suitability of the system at site, prior to the subsequent stages of qualification. This should be appropriately documented.

Installation qualification

- 10.15 IQ should provide documented evidence that the installation was complete and satisfactory, including supporting utilities, where appropriate.
- 10.16 The design specifications, including purchase specifications, drawings, manuals, lists of spare parts and vendor details, should be verified during IQ, as should the configuration specifications for the intended operational environment.
- 10.17 Components installed should be verified, and documented evidence should be provided that components meet specifications, are traceable and are of the appropriate construction material.
- 10.18 Applicable control and measuring devices, identified through impact or risk assessment, should be calibrated.

Operational qualification

- 10.19 OQ should provide documented evidence that utilities, systems or equipment operate in accordance with operational specifications.
- 10.20 Tests should be designed to demonstrate satisfactory operation over the normal operating range, as well as at the limits of its operating conditions. Worst-case conditions may be included in the testing.
- 10.21 Operation controls, alarms, switches, displays and other operational components should be tested.
- 10.22 Measurements made in accordance with a statistical approach should be fully described.

Performance qualification

- 10.23 Normally, PQ should be conducted prior to release of the utilities, systems or equipment. PQ should be performed under conditions simulating the intended use, to provide documented evidence that these can consistently perform in accordance with the specifications under routine use.

Requalification

- 10.24 Utilities, systems and equipment should be maintained in a qualified state. Any changes made to these should be managed through the change-control procedure. The extent of qualification or requalification as a result of such a change should be determined based on principles of risk management.
- 10.25 Requalification should be done based on the identified need and risk management principles. Factors such as the frequency of use, breakdowns, results of operation,

criticality, preventive maintenance, repairs, calibration, and verification may be considered.

- 10.26 Requalification should also be considered after cumulative/multiple changes.
- 10.27 The scope and extent of requalification should be determined when components or parts are replaced.
- 10.28 Where a system or utility or equipment has not been used for an extended period of time, requalification may have to be considered.
- 10.29 Where appropriate, periodic requalification may be performed.

11. Revalidation

- 11.1 Systems should be in place to ensure that procedures, processes and methods remain in a validated state, for example, through periodic review or verification (e.g. in cleaning validation and analytical method validation).
- 11.2 Revalidation should be done based on the identified need and principles of risk management.
- 11.3 Any changes made to, for example, procedures, processes and methods, should be managed through the change-control procedure. The extent of validation or revalidation as a result of such a change should be determined based on principles of risk management.
- 11.4 Where appropriate, periodic revalidation may be performed.

12. Process validation

For recommendations on process validation, see reference (3).

13. Change management

- 13.1 Changes should be controlled in accordance with the appropriate quality management system.
- 13.2 When a change is initiated, consideration should be given to previous changes and the impact of the cumulative effect of the changes. The scope and extent of qualification and validation should be determined based on risk management principles.

14. Deviation management

- 14.1 Any deviation during qualification and validation should be appropriately managed (e.g. investigated, evaluated, the impact assessed, and documented) through an appropriate quality management system.
- 14.2 Corrective actions should be considered.

15. Calibration and verification

- 15.1 Calibration and verification of equipment, instruments and other devices, as applicable, should be initiated during installation qualification, to ensure that the system operates according to the described specifications and because the calibration status could have been affected during transport and installation.
- 15.2 Thereafter, it should be performed at regular intervals in accordance with a calibration programme and SOPs.
- 15.3 Personnel who carry out calibration and preventive maintenance should have appropriate qualification and training.
- 15.4 A calibration programme should be available and should provide information such as calibration standards and limits, responsible persons, calibration intervals, records and actions to be taken when problems are identified.
- 15.5 There should be traceability to standards (e.g. national, regional or international standards) used in the calibration. A valid certificate of calibration should be maintained, which is dated and includes reference to and traceability to, for example, standards used, acceptance limits, uncertainty where applicable, range, calibration due date.
- 15.6 Calibrated equipment, instruments and other devices should be labelled, coded or otherwise identified, to indicate the status of calibration and the date on which recalibration is due.
- 15.7 When the equipment, instruments and other devices have not been used for a certain period of time, their function and calibration status should be verified and shown to be satisfactory before use.
- 15.8 Equipment, instruments and other devices should be calibrated before or on the due date for calibration, to ensure that they are used in a calibrated state.
- 15.9 Where instruments and devices are identified as critical or non-critical, or impacting and non-impacting for the purpose of calibration, documented evidence

of the decision-making process should be available. This should include impact and/or risk assessment.

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Appendix 1

Validation of heating, ventilation and air-conditioning systems

For details on the validation of heating, ventilation and air-conditioning systems, please see:

- Appendix 1: Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018: Annex 8 (WHO Technical Report Series, No. 1010; <https://iris.who.int/bitstream/handle/10665/272452/9789241210195-eng.pdf?sequence=1&isAllowed=y>).

Appendix 2

Validation of water systems for pharmaceutical use

The text of this appendix was previously published as:

- Appendix 2: Validation of water systems for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1).

For details on the validation of water systems for pharmaceutical use, please see:

- WHO good manufacturing practices: water for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-sixth report. Geneva: World Health Organization; 2012: Annex 2 (WHO Technical Report Series, No. 970; Geneva, World Health Organization 2012 (WHO Technical Report Series, No. 970; https://iris.who.int/bitstream/handle/10665/75168/WHO_TRS_970.pdf?sequence=1&isAllowed=y).

Appendix 3

Cleaning validation

The text of this appendix was previously published as:

- Appendix 3: Cleaning validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1).

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1. Principle

- 1.1 The objectives of good manufacturing practices (GMP) include the prevention of possible contamination and cross-contamination of pharmaceutical starting materials and products.
- 1.2 Pharmaceutical products can be contaminated by a variety of substances such as contaminants associated with microbes, previous products (both active pharmaceutical ingredients [APIs] and excipient residues), residues of cleaning agents, airborne materials, such as dust and particulate matter, lubricants and ancillary material, such as disinfectants, and decomposition residues from:
 - product residue breakdown occasioned by, for example, the use of strong acids and alkalis during the cleaning process;
 - breakdown products of the detergents, acids and alkalis that may be used as part of the cleaning process.
- 1.3 Adequate cleaning procedures play an important role in preventing contamination and cross-contamination. Validation of cleaning methods provides documented evidence that an approved cleaning procedure will provide clean equipment, suitable for its intended use.
- 1.4 The objective of cleaning validation is to prove that the equipment is consistently cleaned of product, detergent and microbial residues to an acceptable level, to prevent possible contamination and cross-contamination.
- 1.5 Cleaning validation is not necessarily required for non-critical cleaning such as that which takes place between batches of the same product (or different lots of the same intermediate in a bulk process), or of floors, walls, the outside of vessels, and following some intermediate steps.
- 1.6 Cleaning validation should be considered important in multiproduct facilities and should be performed, among others, for equipment, sanitization procedures and garment laundering.

2. Scope

- 2.1 These guidelines describe the general aspects of cleaning validation, excluding specialized cleaning or inactivation that may be required, for example, for removal of viral or mycoplasmal contaminants in the biological manufacturing industry.
- 2.2 Normally, cleaning validation would be applicable for critical cleaning such as cleaning between manufacturing of one product and another, of surfaces that come into contact with products, drug products and APIs.

3. General

- 3.1 There should be written standard operating procedures (SOPs) detailing the cleaning process for equipment and apparatus. The cleaning procedures should be validated.
- 3.2 The manufacturer should have a cleaning policy and an appropriate procedure for cleaning validation, covering:
 - surfaces that come into contact with the product;
 - cleaning after product changeover (when one pharmaceutical formulation is being changed for another, completely different, formulation);
 - between batches in campaigns (when the same formula is being manufactured over a period of time, and on different days);
 - bracketing products for cleaning validation. (This often arises where products contain substances with similar properties [such as solubility] or the same substance in different strengths. An acceptable strategy is to first manufacture the more dilute form [not necessarily the lowest dose] and then the most concentrated form. There are sometimes “families” of products which differ slightly as to actives or excipients.);
 - periodic evaluation and revalidation of the number of batches manufactured between cleaning validations.
- 3.3. At least three consecutive applications of the cleaning procedure should be performed and shown to be successful, to prove that the method is validated.

4. Cleaning validation protocols and reports

Cleaning validation protocols

- 4.1 Cleaning validation should be described in cleaning validation protocols, which should be formally approved, for example, by the quality control or quality assurance unit.
- 4.2 In preparing the cleaning validation protocol, the following should be considered:
 - disassembly of the system;
 - precleaning;
 - the cleaning agent, concentration, solution volume, water quality;
 - the time and temperature;
 - the flow rate, pressure and rinsing;

- the complexity and design of the equipment;
- training of operators;
- the size of the system.

4.3 The cleaning validation protocol should include:

- the objectives of the validation process;
- the people responsible for performing and approving the validation study;
- the description of the equipment to be used, including a list of the equipment, make, model, serial number or other unique code;
- the interval between the end of production and the commencement of the cleaning procedure (the interval may be part of the validation challenge study itself) – the maximum period that equipment may be left dirty before being cleaned, as well as the establishment of the time that should elapse after cleaning and before use;
- the levels of microorganisms (bioburden);
- the cleaning procedures (documented in an existing SOP, including definition of any automated process) to be used for each product, each manufacturing system or each piece of equipment;
- all the equipment used for routine monitoring, for example, conductivity meters, pH meters and total organic carbon analysers;
- the number of cleaning cycles to be performed consecutively;
- the sampling procedures to be used (direct sampling, rinse sampling, in-process monitoring and sampling locations) and the rationale for their use;
- the data on recovery studies (efficiency of the recovery of the sampling technique should be established);
- the analytical methods (specificity and sensitivity). including the limit of detection and the limit of quantification;
- the acceptance criteria (with rationale for setting the specific limits) including a margin for error and for sampling efficiency;
- Documentation of the choice of cleaning agent and approval by the quality unit, which should be scientifically justified on the basis of, for example:
 - the solubility of the materials to be removed;
 - the design and construction of the equipment and surface materials to be cleaned;
 - the safety of the cleaning agent;
 - the ease of removal and detection;

- the product attributes;
 - the minimum temperature and volume of cleaning agent and rinse solution;
 - the manufacturer's recommendations;
 - revalidation requirements.
- 4.4 Cleaning procedures for products and processes that are very similar do not need to be individually validated. A validation study of the “worst case” may be considered acceptable. There should be a justified validation programme for this approach, referred to as “bracketing”, addressing critical issues relating to the selected product, equipment or process.
- 4.5 Where “bracketing” of products is done, consideration should be given to the type of products and equipment.
- 4.6 Bracketing by product should be done only when the products concerned are similar in nature or property and will be processed using the same equipment. Identical cleaning procedures should then be used for these products.
- 4.7 When a representative product is chosen, this should be the one that is most difficult to clean.
- 4.8 Bracketing by equipment should be done only when it is similar equipment, or the same equipment in different sizes (e.g. 300 L, 500 L and 1000 L tanks). An alternative approach may be to validate the smallest and the largest sizes separately.

Cleaning validation reports

- 4.9 The relevant cleaning records (signed by the operator, checked by production and reviewed by quality assurance) and source data (original results) should be kept. The results of the cleaning validation should be presented in cleaning validation reports stating the outcome and conclusion.

5. Personnel

- 5.1 Personnel or operators who perform cleaning routinely should be trained and effectively supervised.

6. Equipment

- 6.1 Normally, only procedures for the cleaning of surfaces of the equipment that come into contact with the product need to be validated. Consideration should be

given to “non-contact” parts of the equipment into which product or any process material may migrate. Critical areas should be identified (independently from the method of cleaning), particularly in large systems employing semi-automatic or fully automatic clean-in-place systems.

- 6.2 Dedicated equipment should be used for products that are difficult to clean, equipment that is difficult to clean, or products with a high safety risk where it is not possible to achieve the required cleaning acceptance limits using a validated cleaning procedure.
- 6.3 Ideally, there should be one process for cleaning a piece of equipment or system. This will depend on the products being manufactured, whether the cleaning occurs between batches of the same product (as in a large campaign), or whether the cleaning occurs between batches of different products.
- 6.4 The design of equipment may influence the effectiveness of the cleaning process. Consideration should therefore be given to the design of the equipment when preparing the cleaning validation protocol, for example, V-blenders, transfer pumps or filling lines.

7. Detergents

- 7.1 Detergents should facilitate the cleaning process and be easily removable. Detergents that have persistent residues, such as cationic detergents, which adhere very strongly to glass and are difficult to remove, should be avoided where possible.
- 7.2 The composition of the detergent should be known to the manufacturer and its removal during rinsing demonstrated.
- 7.3 Acceptable limits for detergent residues after cleaning should be defined. The possibility of detergent breakdown should also be considered when validating cleaning procedures.
- 7.4 Detergents should be released by quality control and, where possible, should meet local food standards or regulations.

8. Microbiology

- 8.1 The need to include measures to prevent microbial growth and remove contamination where it has occurred should be considered.
- 8.2 There should be documented evidence to indicate that routine cleaning and storage of equipment does not allow microbial proliferation.

- 8.3 The period and conditions for storage of unclean equipment before cleaning, and the time between cleaning and equipment reuse, should form part of the validation of cleaning procedures.
- 8.4 Equipment should be stored in a dry condition after cleaning. Stagnant water should not be allowed to remain in equipment after cleaning.
- 8.5 Control of the bioburden through adequate cleaning and appropriate storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility, and the control of pyrogens in sterile processing. Equipment sterilization processes may not be adequate to achieve significant inactivation or removal of pyrogens.

9. Sampling

General

- 9.1 Equipment should normally be cleaned as soon as possible after use. This may be especially important for operations with topical products, suspensions and bulk drug, or where the drying of residues will directly affect the efficiency of a cleaning procedure.
- 9.2 Two methods of sampling are considered to be acceptable. These are direct surface sampling and rinse samples. A combination of the two methods is generally the most desirable.
- 9.3 The practice of resampling should not be used before or during cleaning and operations and is acceptable only in rare cases. Constant retesting and resampling can show that the cleaning process is not validated, because these retests actually document the presence of unacceptable residue and contaminants resulting from an ineffective cleaning process.

Direct surface sampling (direct method)

Note: This method of sampling is the most commonly used and involves taking an inert material (e.g. cotton wool) on the end of a probe (referred to as a “swab”) and rubbing it methodically across a surface. The type of sampling material used and its potential impact on the test data is important, as the sampling material may interfere with the test (e.g. the adhesive used in swabs has been found to interfere with the analysis of samples).

- 9.4 Factors that should be considered include the supplier of the swab, area swabbed, number of swabs used, whether they are wet or dry swabs, swab handling and swabbing technique.

- 9.5 The location from which the sample is taken should take into consideration the composition of the equipment (e.g. glass or steel) and the location (e.g. blades, tank walls or fittings). Worst-case locations should be considered. The protocol should identify the sampling locations.
- 9.6 Critical areas, that is, those that are hardest to clean, should be identified, particularly in large systems that employ semi-automatic or fully automatic clean-in-place systems.
- 9.7 The sampling medium and solvent used should be appropriate to the task.

Rinse samples (indirect method)

Note: This method allows sampling of a large surface, of areas that are inaccessible or that cannot be routinely disassembled, and provides an overall picture. Rinse samples may give sufficient evidence of adequate cleaning where accessibility of equipment parts can preclude direct surface sampling, and may be useful for checking for residues of cleaning agents, for example, detergents.

- 9.8 Rinse samples should be used in combination with other sampling methods, such as surface sampling.
- 9.9. There should be evidence that samples are accurately recovered. For example, a recovery of >80% is considered good, >50% reasonable and <50% questionable.

Batch placebo method

Note: This method relies on the manufacture of a placebo batch, which is then checked for carry-over of the previous product. It is an expensive and laborious process. It is difficult to provide assurance that the contaminants will be dislodged from the equipment surface uniformly. Additionally, if the particles of the contaminant or residue are large enough, they may not be uniformly dispersed in the placebo batch.

- 9.10 The batch placebo method should be used in conjunction with rinse and/or surface sampling method(s).
- 9.11 Samples should be taken throughout the process of manufacture. Traces of the preceding products should be sought in these samples. (Note that the sensitivity of the assay may be greatly reduced by dilution of the contaminant.)

10. Analytical methods

- 10.1 The analytical methods should be validated before the cleaning validation is performed.

10.2 The methods chosen should detect residuals or contaminants specific for the substance(s) being assayed, at an appropriate level of cleanliness (sensitivity).

10.3 Validation of the analytical method should include as appropriate:

- precision, linearity and selectivity (the latter if specific analytes are targeted);
- limit of detection;
- limit of quantitation;
- recovery, by spiking with the analyte;
- reproducibility.

10.4 The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminants.

10.5 Suitable methods that are sensitive and specific should be used where possible and may include chromatographic methods (e.g. high pressure liquid chromatography; gas chromatography; and high pressure thin-layer chromatography). Other methods may include (alone or in combination) measurement of total organic carbon, pH, or conductivity; ultraviolet spectroscopy; and enzyme-linked immunosorbent assay.

11. Establishing acceptable limits

Note: uniform distribution of contaminants is not guaranteed.

11.1 The acceptance criteria established for contaminant levels in the sample should be practical, achievable and verifiable. The rationale for the residue limits established should be logical, and based on the knowledge of the materials involved.

11.2 Each situation should be assessed individually. The manner in which limits are established should be carefully considered. In establishing residual limits, it may not be adequate to focus only on the principal reactant, because other chemical variations may be more difficult to remove.

11.3 Where necessary, screening using thin-layer chromatography should be performed in addition to chemical analyses.

11.4 There should be no residue from the previous product, from reaction by-products and degradants, or from the cleaning process itself (e.g. detergents or solvents).

11.5 The limit-setting approach can:

- be product-specific;
 - group products into families and choose a worst-case product;
 - group products into groups according to risk, for example, very soluble products, products with similar potency, highly toxic, or difficult-to-detect products;
 - use different safety factors for different dosage forms, based on physiological response (this method is essential for potent materials).
- 11.6 Limits may be expressed as a concentration in a subsequent product (parts per million – ppm), limit per surface area ($\mu\text{g}/\text{cm}^2$), or in rinse water as ppm.
- 11.7 The sensitivity of the analytical methods should be defined, to enable reasonable limits to be set.
- 11.8 The rationale for selecting limits for carry-over of product residues should meet defined criteria.
- 11.9 The three most commonly used criteria are:
- visually clean: no residue should be visible on equipment after cleaning. Spiking studies should determine the concentration at which most active ingredients are visible. This criterion may not be suitable for high-potency, low-dosage drugs;
 - no more than 10 ppm of one product will appear in another product (basis for heavy metals in starting materials);
 - no more than 0.1% of the normal therapeutic dose of one product will appear in the maximum daily dose of a subsequent product.
- 11.10 The most stringent of three options should be used.
- 11.11 Certain allergenic ingredients (e.g. penicillins and cephalosporins) and highly potent material (e.g. anovulant steroids, potent steroids and cytotoxics) should be undetectable by the best available analytical methods. (In practice, this may mean that dedicated manufacturing facilities should be used for the manufacture and processing of such products.)

Appendix 4

Analytical procedure validation

Background

This is a revision of the previous publication:

- Supplementary guidelines on good manufacturing practices: validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Appendix 4: Analytical method validation. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1).

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1. Principle

- 1.1 This appendix presents some information on the principles and characteristics that should be considered during validation and life-cycle management of analytical procedures. Approaches other than those specified in this appendix may be followed and may be acceptable. Manufacturers should choose the validation protocol and procedures most suitable for testing of their product. Owing to their complex nature, analytical procedures for biological and biotechnological products may, in some cases, be approached differently than is indicated in this document.
- 1.2 Validation is the documented evidence that the analytical procedure is suitable for its intended purpose.
- 1.3 Analytical procedures, whether or not they indicate stability, should be validated.
- 1.4 Analytical procedures should be validated before being used for quality control purposes.
- 1.5 The recommendations as provided for in good practices (GXP) for pharmaceutical quality control laboratories (1), guidance on good data and record management practices (2) and guidelines for transfer of technology (3) should be followed, where applicable, when analytical procedure validation is organized and planned.

2. General

- 2.1 There should be specifications (a list of tests, references to analytical procedures and appropriate acceptance criteria) for both materials and products. The tests to be performed should be described in the documentation.
- 2.2 Acceptance criteria and test methods described in pharmacopoeias (“pharmacopoeial methods”), or suitably developed acceptance criteria or test methods (“non-pharmacopoeial methods”), as approved by the national regulatory authority (NRA), may be used.
- 2.3 Well-characterized reference standards, with documented suitability for the intended use, should be used in validation studies as well as in analysis.
- 2.4 The results of analytical procedures should be reliable, that is, attributable, legible, contemporaneous, original, accurate and reproducible.
- 2.5 The procedure should be followed, to continually assure that it meets the predefined criteria over its life-cycle.
- 2.6 Trend analysis and risk assessment should be considered at intervals, to ensure that the procedure is appropriate for its intended application.

- 2.7 Changes to procedures should be managed in accordance with the authorized change-control procedure. When analytical procedures are to be used by another laboratory and method transfer is not possible, the variability of reference standards and other factors, such as changes in the process for synthesis of the drug substance, changes in the composition of the finished product, changes in the analytical procedure, or changes to major pieces of equipment or instruments, should be considered. These should be understood, controlled and, where possible, reduced. Verification or revalidation should be considered, where appropriate.
- 2.8 The need and scope of verification or degree of revalidation depend on the nature of the change(s) and the outcome of risk assessment.
- 2.9 There should be evidence that the analysts, who are responsible for certain tests, are appropriately qualified to perform those analyses (“analyst proficiency”) and that the equipment and instruments involved are appropriately qualified.
- 2.10 The data obtained during procedure validation and verification (including their associated metadata) should be considered covered by GXP requirements and are expected to follow the principles of GXP for data and record management (2).
- 2.11 When computerized systems are used to obtain and process data relating to procedure validation and verification, they should comply with the principles enunciated in *Appendix 5. Validation of computerized systems*.
- 2.12 Adequate attention should be paid to sample preparation. The description of this step should be as detailed as possible, especially if it can have a significant impact on test results (e.g. particular attention should be paid to details such as sonication time, sonication bath temperature and mixing, conditions of shaking, type of a shaker, and samples where demixing is known to occur). As sample preparation is an integral part of the analytical procedures, this step should be incorporated in the validation experiments as appropriate.

3. Pharmacopoeial methods

- 3.1 When pharmacopoeial methods are used, evidence should be available to prove that such methods are suitable for routine use in the laboratory (verification – see Section 6).
- 3.2 Pharmacopoeial methods used for determination of content or impurities in pharmaceutical products should also have been demonstrated to be specific with respect to the product under consideration (no placebo interference).

4. Non-pharmacopoeial methods

- 4.1 Non-pharmacopoeial methods should be appropriately validated.

5. Procedure validation

- 5.1 Validation should be performed in accordance with the validation protocol. The protocol should include procedures and acceptance criteria for all characteristics. The results should be documented in the validation report.
- 5.2 Justification should be provided when non-pharmacopoeial methods are used, if pharmacopoeial methods are available.
- 5.3 Test methods should be described in detail and should provide sufficient information to allow properly trained analysts to perform the analysis in a reliable manner. As a minimum, the description should include the chromatographic conditions (in the case of chromatographic tests), reagents needed, sample preparation, reference standards, the formulae for the calculation of results and system suitability tests.

6. Procedure verification

- 6.1 Procedure verification consists of partial validation. It should be performed for already validated analytical procedures under the following circumstances:
- when an already validated procedure is used on a product for the first time (e.g. in case of a change in active pharmaceutical ingredient [API] supplier, change in the method of synthesis or after reformulation of a drug product);
 - when an already validated procedure is used for the first time in a laboratory that is different from the one that validated the procedure (in some cases, method transfer may be preferable).
- 6.2 Procedure verification may include only the validation characteristics of relevance to the particular change. The selection of characteristics for verification depends on the procedure and its intended use and should be justified. For instance, in the case of a change in API supplier, the only expected difference would be in the impurity profile or solubility of the API, and therefore, for a procedure for related substances, there should be an appropriate verification that the procedure is able to detect and quantitate all potential impurities, even the late-eluting ones. Specificity should be among the tests considered (see Sections 9 for more detail).
- 6.3 Procedure verification is suitable in lieu of validation for pharmacopoeial methods.

7. Procedure revalidation

- 7.1 Procedures should be maintained in a validated state over the life-cycle of the procedure (see point 2.5). Whenever there are changes made to the analytical procedure, the impact assessment should be conducted and revalidation of the procedure should be considered. For example for a high-performance liquid chromatography (HPLC) method, changes requiring revalidation may include (please refer to *The International Pharmacopoeia* (4) and other pharmacopoeias for the acceptance limits beyond which revalidation must be performed):
- changes to the mobile phase;
 - changes to the column;
 - changes to the temperature of the column;
 - changes to the concentration/composition of the samples and standards;
 - changes to the detector (change in detector type, for example, if going from ultraviolet-visible detection to fluorimetry, or wavelength of detection).
- 7.2 In the case of repeated system suitability failures or when obtaining doubtful results, an investigation of the root cause should be performed. In the case that the procedure is identified as being the root cause, the appropriate changes should be made and the procedure revalidated.
- 7.3 Periodic revalidation of analytical procedures should be considered and the interval should be scientifically justifiable.
- 7.4 It is acceptable for revalidation to include only the validation characteristics of relevance to the particular change and procedure.

8. Method transfer

- 8.1 During method transfer, documented evidence should be established to prove that a method has equivalent performance when used in a laboratory that is different from the one where it has been validated.
- 8.2 Generally, it should be performed by comparing a set of results obtained by one laboratory to those obtained by another laboratory to which the method is being transferred.
- 8.3 The two sets of results should be compared and the differences between them should be within an acceptable range, which is predefined in the transfer protocol.

- 8.4 Method transfer should be performed before the testing of samples, with a view to obtaining critical data for a dossier, such as process validation or stability studies, or before being applied for routine use.
- 8.5 A predefined protocol should be followed, which includes at least: a title, objective, scope, responsibilities of the sending unit and the receiving unit; a specification of materials and methods; the experimental design and acceptance criteria; documentation (including information to be supplied with the results, and report forms to be used, if any); procedure for the handling of deviations; references; and details of reference samples (starting materials, intermediates and finished products). The protocol should be authorized and dated.
- 8.6 In the case of independent testing by a separate entity, such as a national quality control testing laboratory that is testing samples on its market, method transfer is not always possible. It is not considered an obligation but may be considered as an optional step when encountering difficulties in applying any particular method. See *WHO guidelines on transfer of technology in pharmaceutical technology* (3) for further reference.

9. Characteristics of analytical procedures

- 9.1 Characteristics that should be considered during validation of analytical procedures include:

- accuracy;
- precision;
- robustness;
- linearity;
- range;
- specificity;
- detection limit;
- quantitation limit.

This list should be considered typical but occasional exceptions should be dealt with on a case-by-case basis.

- 9.1.1 *Accuracy* is the degree of agreement of test results with the true value, or the closeness of the results obtained by the procedure to the true value. It is normally established on samples of the material to be examined that have been prepared to quantitative accuracy. Accuracy should be established across the specified range of the analytical procedure, for example, three concentrations/three replicates each.

Note: It is acceptable to use a “spiked” placebo where a known quantity or concentration of a reference standard is used.

9.1.2 *Precision* is the degree of agreement among individual results. The complete procedure should be applied repeatedly to separate, identical samples drawn from the same homogeneous batch of material. It should be measured by the scatter of individual results from the mean (good grouping), and is usually expressed as the standard deviation or relative standard deviation.

Repeatability should be assessed using a minimum of nine determinations covering the specified range for the procedure, for example, three concentrations/three replicates each, or a minimum of six determinations at 100% of the test concentration.

Intermediate precision expresses within-laboratory variations (usually on different days, with different analysts and different equipment). If reproducibility is assessed, a measure of intermediate precision is not required.

Reproducibility expresses precision between laboratories.

9.1.3 *Robustness* is the ability of the procedure to provide analytical results of acceptable accuracy and precision under a variety of conditions. The results from separate samples are influenced by changes in the operational or environmental conditions. Robustness should be considered during the development phase and should show the reliability of an analysis when deliberate variations are made in method parameters.

Factors that can have an effect on robustness when performing chromatographic analysis include:

- stability of the test and standard samples and solutions;
- reagents (e.g. different suppliers);
- different columns (e.g. different lots and/or suppliers);
- variation of extraction time;
- variations of pH;
- variations in mobile-phase composition;
- temperature;
- flow rate.

The variation of extraction time and stability of analytical solutions are of particular importance.

- 9.1.4 *Linearity* indicates the ability to produce results that are directly proportional to the concentration of the analyte in samples. A series of samples should be prepared in which the analyte concentrations span the claimed range of the procedure. If there is a linear relationship, test results should be evaluated by appropriate statistical methods. A minimum of five concentrations should be used. If linearity is not attainable, a nonlinear model may be used.
- 9.1.5 *Range* is an expression of the lowest and highest levels of analyte for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity. The specified range is normally derived from linearity studies.
- 9.1.6 *Specificity (selectivity)* is the ability to measure unequivocally the desired analyte in the presence of components such as excipients and impurities that may also be expected to be present. An investigation of specificity should be conducted during the validation of identification tests, the determination of impurities and the assay. The procedures used to demonstrate specificity depend on the intended objective of the analytical procedure.
- 9.1.7 *Detection limit (limit of detection)* is the smallest quantity of an analyte that can be detected, and not necessarily determined, in a quantitative fashion. Approaches may include instrumental or non-instrumental procedures and could include those based on:
- visual evaluation;
 - signal-to-noise ratio;
 - standard deviation of the response and the slope;
 - standard deviation of the blank;
 - calibration curve.
- 9.1.8 *Quantitation limit (limit of quantitation)* is the lowest concentration of an analyte in a sample that may be determined with acceptable accuracy and precision. Approaches may include instrumental or non-instrumental procedures and could include those based on:
- visual evaluation;
 - signal-to-noise ratio;
 - standard deviation of the response and the slope;
 - standard deviation of the blank;
 - calibration curve.

9.2 Characteristics (*including tests*) that should be considered when using different types of analytical procedures are summarized in Table A3.4.1. More details can be found in the guidelines listed in the Further reading section at the end of this appendix.

Table 3.4.1
Characteristics to consider during analytical validation

Type of analytical procedure	Testing for impurities			
	Identification	Quantitative tests	Limit tests	Assay^a
Characteristics				
Accuracy	—	+	—	+
Precision				
Repeatability	—	+	—	+
Intermediate precision ^b	—	+	—	+
Specificity	+	+	+	+
Detection limit	—	— ^c	+	—
Quantitation limit	—	+	—	—
Linearity	—	+	—	+
Range	—	+	—	+

— Characteristic is not normally evaluated; + characteristic should normally be evaluated.

^a dissolution (measurement only) or content/potency.

^b In cases where a reproducibility study has been performed, intermediate precision is not needed.

^c May be needed in some cases.

9.3 Statistical analysis used to evaluate validation characteristics against predetermined acceptance criteria should be appropriate for the intended evaluation. Statistical analysis should be performed using appropriately validated software. Alternatively, if validated software is not used, the calculations must be verified to be correct. An appropriate number of samples to provide adequate statistical power and range should be considered.

10. System suitability testing

Note: System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations

and samples to be analysed constitute an integral system that can be evaluated as such. System suitability test parameters that need to be established for a particular procedure depend on the type of procedure being evaluated, for instance, a resolution test for an HPLC procedure.

- 10.1 System suitability testing should be done as appropriate and defined in the test procedure.
- 10.2 System suitability runs should include only reference standards or established standards of known concentration, to provide an appropriate comparator for the potential variability of the instrument. The sample material or product under test should not be used as a standard to evaluate the suitability of the system (see *General guidelines for the establishment, maintenance and distribution of chemical reference substances* (5)).

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Further reading

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Appendix 5

Validation of computerized systems

Background

This is a revision of the previous publication:

- Supplementary guidelines on good manufacturing practices: validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Appendix 5: Validation of computerized systems. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1).

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1. Introduction and scope

- 1.1 Computerized systems should be validated in accordance with the principles of quality risk management and the level of validation should be commensurate with the identified risks, complexity and intended use. This guide applies to systems used in good manufacturing practices (GMP) (1) but may be extended to systems used in all good practices (GXP) activities, as appropriate.
- 1.2 The purpose of validation is to confirm that the specifications of a computerized system conform to the user's needs and are fit for intended use, by examination and provision of documented and objective evidence that the particular requirements can be consistently fulfilled. Validation should establish confidence in the accuracy, reliability and consistency in the performance of the system, and should also ensure that all necessary technical and procedural controls are implemented, confirming compliance with good documentation practices for electronic data generated by the system (1).
- 1.3 System elements that need to be considered in validation of a computerized system include computer hardware and software, and related equipment, IT infrastructure and operating system environment, and documentation of procedures and systems, as appropriate, including user manuals. Persons should be appropriately trained and qualified, including but not limited to, developers, end-users, system application administrators, network engineers, database administrators and data managers. Computerized system validation activities should address both system functionality and configuration, as well as any custom-developed elements.
- 1.4 Computerized systems should be maintained throughout the system life-cycle, in a validated state, with risk-based controls for the operational phase, which may include, but are not limited to, system planning; preparation and verification of standard operating procedures (SOPs) and training programmes; system operation and maintenance, including handling of software and hardware updates; monitoring and review; change management; and incident reporting, followed by system retirement.
- 1.5 Depending on the types of systems or typical applications, such as process control systems (distributed control system [DCS], programmable logic controller [PLC], supervisory control and data acquisition [SCADA]); laboratory information management systems (LIMS); laboratory instrument control systems; and business systems (enterprise resource planning [ERP], manufacturing resource planning [MRP II]) used by the manufacturer. Documentation covering, but not limited to, the following information and supporting process should be accessible on-site for review:

- purpose and scope;
- roles and responsibilities;
- validation approach;
- risk management approach;
- approved system requirement/specifications;
- system acceptance criteria;
- supplier selection and assessment;
- configuration management and change-control procedures;
- backup and recovery (application and data);
- error handling and corrective action;
- business continuity plan and disaster recovery;
- maintenance and support;
- data security, including cybersecurity;
- validation deliverables and documentation.

2. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

archiving. Archiving is the process of protecting records from the possibility of being further altered or deleted, and storing these records under the control of independent data management personnel throughout the required retention period. Archived records should include, for example, associated metadata and electronic signatures.

audit trail. The audit trail is a form of metadata that contains information associated with actions that relate to the creation, modification or deletion of GXP records. An audit trail provides for secure recording of life-cycle details, such as creation, additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or overwriting the original record. An audit trail facilitates the reconstruction of the history of such events relating to the record, regardless of its medium, including the “who”, “what”, “when” and “why” of the action. For example, in a paper record, an audit trail of a change would be documented via a single-line cross-out that allows the original entry to remain legible and documents the initials of the person making the change, the date of the change and the reason for the change, as required to substantiate and justify the change. In electronic records, secure, computer-generated, time-stamped audit trails should allow for reconstruction of the course of events relating to the creation, modification and deletion of electronic data. Computer-generated audit trails should retain the original entry and document the user identification and the time/date stamp of the action, as well

as the reason for the change, as required to substantiate and justify the action. Computer-generated audit trails may include discrete event logs, history files, database queries or reports, or other mechanisms that display events related to the computerized system, specific electronic records or specific data contained within the record.

automatic or live update. A process used to bring up-to-date software and system functionalities in a silent or announced way. More specifically, the update takes place automatically with or without the user's knowledge.

backup. A backup means a copy of one or more electronic files created as an alternative in case the original data or system are lost or become unusable (e.g. in the event of a system crash or corruption of a disk). It is important to note that backup differs from archiving, in that backup copies of electronic records are typically only temporarily stored for the purposes of disaster recovery and may be periodically overwritten. Such temporary backup copies should not be relied upon as an archiving mechanism.

business continuity plan. A documented plan that defines the ongoing process supported by management and funded to ensure that the necessary steps are taken to identify the impact of potential losses, maintain viable recovery strategies and recovery plans, and assure continuity of services through personnel training, plan testing and maintenance.

cloud based. A model for enabling on-demand network access to a shared pool of configurable computing resources that can be rapidly provisioned and released with minimal management effort or service provider interaction. These computing resources should be appropriately qualified.

computerized system. A computerized system collectively controls the performance and execution of one or more automated processes and/or functions. It includes computer hardware, software, peripheral devices, networks and documentation, for example, manuals and standard operating procedures, as well as personnel interacting with hardware and software.

computerized systems validation. Confirmation by examination and provision of objective and documented evidence that a computerized system's predetermined specifications conform to user needs and intended use and that all requirements can be consistently fulfilled.

commercial off-the-shelf software (COTS). A vendor-supplied software component of a computerized system for which the user cannot claim complete control of the software life-cycle.

configuration management. A discipline applying technical and administrative direction and surveillance to identify and document the functional and physical characteristics of a configuration item, control changes to those characteristics, record and report change processing and implementation status, and verify compliance with specified requirements.

data. All original records and true copies of original records, including source data and metadata, and all subsequent transformations and reports of these data, which

are generated or recorded at the time of the GMP activity and allow full and complete reconstruction and evaluation of the GMP activity. Data should be accurately recorded by permanent means at the time of the activity. Data may be contained in paper records (such as worksheets and logbooks), electronic records and audit trails, photographs, microfilm or microfiche, audio or video files or any other media whereby information related to GMP activities is recorded.

data integrity. The degree to which data are complete, consistent, accurate, trustworthy and reliable and to which these characteristics of the data are maintained throughout the data life-cycle. The data should be collected and maintained in a secure manner, such that they are attributable, legible, contemporaneously recorded, original or a true copy and accurate. Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices (1).

data life-cycle. All phases of the process by which data are created, recorded, processed, reviewed, analysed and reported, transferred, stored and retrieved and monitored, until retirement and disposal. There should be a planned approach to assessing, monitoring and managing the data and the risks to those data, in a manner commensurate with potential impact on patient safety, product quality and/or the reliability of the decisions made throughout all phases of the data life-cycle.

disaster recovery. A documented process or set of procedures to recover and protect a business IT infrastructure in any event causing the system to be unavailable. It appropriately defines resources and actions to be taken before, during and after a disaster, to return the system to operational use.

functional specifications. The functional specifications define functions and technological solutions that are specified for the computerized system, based upon technical requirements needed to satisfy user requirements (e.g. specified bandwidth required to meet the user requirement for anticipated system usage).

legacy system. This refers to a mature computer system, programming language, application software, or processes that are used instead of available upgraded versions, and that have not been qualified according to current regulatory requirements.

master data. A single source of business data used across multiple systems, applications and processes and subject to change control to ensure accuracy throughout the data life-cycle.

metadata. Metadata are data about data that provide the contextual information required to understand those data. These include structural and descriptive metadata. Such data describe the structure, data elements, interrelationships and other characteristics of data. They also permit data to be attributable to an individual. Metadata necessary to evaluate the meaning of data should be securely linked to the data and subject to adequate review. For example, in weighing, the number 8 is meaningless without metadata, such as, the unit, milligram, gram, kilogram, etc. Other examples

of metadata include the time/date stamp of an activity, the operator identification (ID) of the person who performed an activity, the instrument ID used, processing parameters, sequence files, audit trails and other data required to understand data and reconstruct activities.

production environment. For regulated computerized systems, the production environment is the business and computing operating environment in which the computerized system is being used for GMP-regulated purposes.

regression analysis and testing. A documented software verification and validation task to determine the extent of verification and validation analysis and testing that must be repeated when changes are made to any previously examined software component or system.

system life-cycle. The period of time that starts when a computerized system is conceived and ends when the system is retired and decommissioned, taking into consideration regulatory requirements. The system life-cycle typically includes a planning phase; a development phase that includes a design phase and a programming and testing phase; a qualification and release phase that includes a system integration and testing phase; a validation phase; a release phase; an operation and maintenance phase; and, finally, a system retirement phase.

user acceptance testing. Verification of the fully configured computerized system installed in the production environment (or in a test environment equivalent to the production environment) to perform, as intended, in the business process when operated by end-users trained in end-user SOPs that define system use and control. User acceptance testing (UAT) may be a component of the performance qualification (PQ) or a validation step separate from the PQ.

user requirements specification. The user requirements specification (URS), if prepared as a separate document, is a formal document that defines the requirements for use of the computerized system in its intended production environment.

3. Computerized system validation protocols and reports

3.1 A computerized system needs to be validated according to an approved protocol and a final report including results and conclusions, prior to routine use. All validation documentation should be appropriately retained.

Validation protocol

- 3.2 Validation should be executed in accordance with the validation protocol and applicable written procedures.
- 3.3 A validation protocol should define the objectives and the validation strategy, including roles and responsibilities and documentation and activities to be

performed. The protocol should at least cover the scope, risk management approach, specification, acceptance criteria, testing, review, personnel training and release of the computerized system for GMP use.

- 3.4 The validation protocol should be tailored to the system type, impact, risks and requirements applicable to the system for which it governs validation activities.

Validation report

- 3.5 A validation report should be prepared, summarizing system validation activities.
- 3.6 The report should make reference to the protocol, outline the validation process, and include an evaluation and conclusion of results. Any changes or deviations from the validation protocol and applicable written procedures should be described and assessed, and justification for their acceptance or rejection should be documented. Deviations should be investigated and a root cause determined. A validation report should also include a summary of procedures and training.
- 3.7 Test results should be recorded, reviewed, analysed and compared against the predetermined acceptance criteria. All critical and major test discrepancies that occurred during the verification/validation testing should be investigated and resolved. If critical and major test discrepancies are accepted after investigation, they should be appropriately justified.
- 3.8 The conclusion of the report should state whether or not the outcome of the validation was considered successful and should make recommendations for future monitoring where applicable. The report should be approved after appropriately addressing any issue identified during validation, and the system should then be released for routine GMP use.

4. Supplier management

- 4.1 When third parties (e.g. suppliers, service providers) are used, such as to provide, install, configure, validate, maintain, modify or retain a computerized system or related service, or for data processing or system components, including cloud-based systems, an evaluation of the supplier, supplied system or service, and the supplier's quality systems should be conducted and recorded. The scope and depth of this evaluation should be based upon risk management principles.
- 4.2 The competence and reliability of a supplier are key factors when selecting a product and/or service provider. Supplier management is an ongoing process that requires periodic assessment and review of the system or service provided. Supplier evaluation activities may include, but are not limited to: completion of a quality-

related questionnaire by the supplier; gathering of supplier documentation related to system development, testing and maintenance, including supplier procedures, specifications, system architecture diagrams, test evidence, release notes and other relevant supplier documentation; an on-site audit of the supplier's facilities, which may be conducted based on risk principles to evaluate the supplier's system life-cycle control procedures, practices and documentation.

- 4.3 A contract should be in place between the manufacturer and the supplier and/or the service provider, defining the roles and responsibilities and quality procedures for both parties, throughout the system life-cycle. The contract acceptor should not pass to a third party any of the work entrusted to her/him under the contract, without the manufacturer's prior evaluation and approval of the arrangements.

5. Requirements specifications

- 5.1 Requirements specifications should be written to document user requirements and functional or operational requirements and performance requirements. Requirements may be documented in separate user requirements specification (URS) and functional requirements specifications (FRS) documents, or in a combined document.

User requirements specifications

- 5.2 The authorized URS document, or equivalent, should describe the intended uses of the proposed computerized system and should define critical data and data life-cycle controls that will assure consistent and reliable data throughout the processes by which data are created, processed, transmitted, reviewed, reported, retained and retrieved and eventually disposed. The URS should be written in a way to ensure that the data will meet regulatory requirements, such as the World Health Organization (WHO) *Guidance on good data and record management practices* (1).

- 5.3 Other aspects to be included in the URS may include, but are not limited to:

- the transaction or data to be entered, processed, reported, stored and retrieved by the system, including any master data and other data considered to be the most critical to system control and data output;
- the flow of data, including that of the business process(es) in which the system will be used, as well as the physical transfer of the data from the system to other systems or network components. Documentation of data flows and data process maps is recommended, to facilitate the assessment and mitigation and control of data integrity risks across the actual, intended data process(es);

- networks and operating system environments that support the data flows;
- the system interfaces with other systems and the overall security;
- the operating program;
- synchronization and security controls of time/date stamps;
- controls of both the application software as well as operating systems, to assure system access only to authorized persons;
- controls to ensure that data will be attributable to unique individuals (e.g. to prohibit use of shared or generic log-in credentials);
- controls to ensure that data related to GMP purposes is legibly and contemporaneously recorded to durable (“permanent”) media at the time of each step and event, and controls that enforce the sequencing of each step and event (e.g. controls that prevent alteration or deletion of data in temporary memory in a manner that would not be documented);
- controls that assure that all steps that create, modify or delete electronic data related to GMP purposes will be recorded in independent, computer-generated audit trails or other metadata, or alternate documents that record the “what” (e.g. original entry), “who” (e.g. user ID), “when” (e.g. time/date stamp) and “why” (e.g. reason) of the action;
- backups and the ability to restore the system and data from backups;
- the ability to archive and retrieve the electronic data in a manner that assures that the archive copy preserves the full content of the original electronic data set, including all metadata needed to fully reconstruct the GMP activity. The archive copy should also preserve the meaning of the original electronic data set;
- input/output checks, including implementation of procedures for the review of original electronic data and metadata, such as audit trails;
- electronic signatures;
- alarms and flags that indicate alarm conditions and invalid and altered data, in order to facilitate detection and a review of these events;
- system documentation, including system specifications documents, user manuals and procedures for system use, data review and system administration;
- system capacity and volume requirements, based upon the predicted system usage and performance requirements;
- performance monitoring of the system;
- controls for orderly system shutdown and recovery;
- business continuity.

- 5.4 The extent and detail of the requirements should be commensurate with the operational risk and the complexity of the computerized system. User requirements should be specific and phrased in a way that supports their testing or verification within the context of the computerized system.

Functional specifications

- 5.5 Functional specifications should describe in detail the functions, performance and interfaces of the computerized system, based upon the technical requirements needed to satisfy user requirements, and should be linked to user specifications.
- 5.6 The functional specifications provide a basis for the system design and configuration specifications. Functional specifications should consider requirements for operation of the computerized system in the intended computing environment, such as functions provided by supplier-provided software, as well as functions required for user business processes that are not met by commercial off-the-shelf software (COTS) functionality, and default configurations that will require custom code development. Network infrastructure requirements should also be taken into account. Each described function should be verifiable.
- 5.7 Personnel access roles that provide the ability and/or authorization to write, alter or access programs or configuration should be defined and qualified. There should be appropriate segregation of roles between personnel responsible for the business process and personnel for system administration and maintenance.

6. System design and configuration specifications

- 6.1 System design and configuration specifications should be developed based on user and functional requirements. Specification of design parameters and configuration settings (separate or combined) should ensure data integrity and compliance with the WHO *Guidance on good data and record management practices* (1).
- 6.2 System design and configuration specifications should provide a high-level system description, as well as an overview of the system's physical and logical architecture, and should map out the system business process and relevant work flows and data flows if these have not already been documented in other requirements specifications documents.
- 6.3 The system design and configuration specifications may include, as applicable, a software design specification, in case of code development, and configuration specifications of the software application parameters, such as security profiles, audit trail configuration, data libraries and other configurable elements.

- 6.4 In addition, the system design and configuration specifications may also include, based upon risk, the hardware design and its configuration specifications, as well as that of any supporting network infrastructure.
- 6.5 System design and configuration specifications should include secure, protected, independent computer-generated audit trails to track configuration changes to critical settings in the system.

7. Design qualification

- 7.1 Following design qualification (DQ), a review should be conducted to verify that the proposed design and configuration of the system is suitable for its intended purpose and will meet all applicable user and functional specifications.
- 7.2 It may include a review of supplier documentation, if applicable, and verification that requirements specifications are traceable to proposed design and configuration specifications. The DQ review should be documented.

8. System development and project implementation

- 8.1 Once the system requirements and the system design and configuration are specified and verified, where applicable, system development activities may begin. The development activities may occur as a dedicated phase following completion of specification of system requirements, design and configuration. Alternatively, development activities may occur iteratively as requirements are specified and verified (such as when prototyping or rapid-development methodologies are employed).

Supplier-provided systems

- 8.2 For supplier-provided systems, the development controls for the supplier-provided portion of the computerized system should be assessed during the supplier evaluation or supplier qualification. For supplier-provided systems that include custom components (such as custom-coded interfaces or custom report tools) and/or require configuration (such as configuration of security profiles in the software or configuration of the hardware within the network infrastructure), the system should be developed under an appropriate documented quality management system.

Custom-developed systems

- 8.3 For custom-developed and configurable systems, the system should be developed under an appropriate documented quality system. For these systems or modules, the quality management system controls should include development of code in

accordance with documented programming standards, review of code for adherence to programming standards, and design specifications and development testing that may include unit testing and module/integration testing.

- 8.4 System prototyping and rapid, agile development methodologies may be employed during the system build and development testing phase. There should be an adequate level of documentation of these activities.

Preparation for the system qualification phase

- 8.5 The system development and build phase should be followed by the system qualification phase. This typically consists of installation, operational and performance testing. The actual qualification required may vary depending on the scope of the validation project, as defined in the validation protocol and based upon a documented and justified risk assessment.
- 8.6 Prior to the initiation of the system qualification phase, the software program and requirements and specifications documents should be finalized and subsequently managed under formal change control.
- 8.7 Persons who will be conducting the system qualification should be trained to adhere to the following requirements for system qualification:
- test documentation should be generated to provide evidence of testing;
 - test documentation should comply with good documentation practices;
 - any discrepancies between actual test results and expected results should be documented and adequately resolved, based upon risk prior to proceeding to subsequent test phases.

9. Installation qualification

- 9.1 Installation qualification (IQ) – also referred to as installation verification testing – should provide documented evidence that the computerized system, including software and associated hardware, is installed and configured in the intended system test and production environments, according to written specifications.
- 9.2 The IQ will verify, for example, that the computer hardware on which the software application is installed has the proper firmware and operating system, that all components are present and in the proper condition, and that each component is installed per the manufacturer or developer instructions.
- 9.3 IQ should include verification that configurable elements of the system are appropriately set as specified. Where appropriate, this could also be done during operational qualification (OQ).

10. Operational qualification

10.1 The OQ – or operational/functional verification testing – should provide documented evidence that software and hardware function as intended over anticipated operating ranges.

10.2 Functional testing should include, based upon risk:

- challenges on the system's ability to do what it should do, including verification that significant alerts and error messages are raised based upon alarm conditions and according to specifications;
- an appropriate degree of testing (such as boundary, range, limit, and nonsense entry testing), to verify that the system appropriately handles erroneous entries or erroneous use.

11. Standard operating procedures and training

11.1 Prior to conducting of the PQ and UAT, and prior to release of the computerized system, there should be adequate written procedures and documents and training programmes created defining system use and control. These may include supplier-provided user manuals as well as SOPs and training programmes developed in house.

11.2 Procedures and training programmes that should be developed include, but are not necessarily limited to:

- system use procedures that address:
 - routine operation and use of the system in the intended business process(es);
 - review of the electronic data and associated metadata (such as audit trails) and how the source electronic records will be reconciled with printouts, if any;
 - mechanisms for signing electronic data;
 - system training requirements prior to being granted system access;
- system administration procedures that address:
 - granting disabling and review of user access and maintaining security controls;
 - backup/restore;
 - archiving/retrieval;
 - disaster recovery and business continuity;

- change management;
- incident and problem management;
- system maintenance.

12. Performance qualification and user acceptance testing

- 12.1 PQ, which includes UAT, should be conducted to verify the intended system use and administration defined in the URS and DQ, or equivalent document.
- 12.2 The PQ should be conducted in the live environment (controls for restricted release for GMP use may be necessary) or in a test environment that is functionally equivalent to the live environment in terms of overall software and hardware configuration.
- 12.3 PQ testing should also include, as applicable, an appropriate degree of stress/load/volume testing, based upon the anticipated system use and performance requirements in the production environment. Such testing may also be performed during OQ if appropriately justified.
- 12.4 In addition, an appropriate degree of end-to-end or regression testing of the system should be conducted to verify the system performs reliably when system components are integrated in the fully configured system deployed in the production environment.
- 12.5 UAT should be conducted by system users, to verify the adequacy of the system, use of SOPs and training programmes. The UAT should include verification of the ability to generate and process only valid data within the computerized system, including the ability to efficiently review electronic data and metadata, such as audit trails. SOPs should be finalized and approved upon completion of performance qualification.

Legacy systems

- 12.6 The continued use of a legacy system should be justified by demonstrating the system continues to be relevant to the GMP process being supported and by ensuring adequate validation of the system (i.e. hardware, software, peripheral devices, networks) has been performed.
- 12.7 The validation approach to be taken should aim at providing data and information to justify and support the retrospective qualification of the system. It should demonstrate that the system remains in a state of control and is fit for its intended

use and, where necessary, it should include an approach for retrospective qualification of the system with relevant evidence.

- 12.8 A risk assessment should be undertaken to determine the criticality of the system to the process or operation being supported, and a gap analysis should identify the level of completeness of existing qualification documentation (e.g. URS, IQ/OQ/PQ, SOPs) and state of system control, operation and maintenance.
- 12.9 For legacy systems, development documentation and records appropriate for validation may not be available. Nevertheless, the strategy should be consistent with validation principles where assurance is established, based on compilation and formal review of the history of use, maintenance, error report and change-control system records. These activities should be based on documented URS. If historical data do not encompass the current range of operating parameters, or if there have been significant changes between past and current practices, then retrospective data would not of themselves support validation of the current system.
- 12.10 The validation exercise should demonstrate that user requirements and system description have been appropriately established, as well as providing evidence that the system (i.e. hardware, software, peripheral devices, networks, processes) has been qualified and accepted and that GMP requirements are met.

13. System operation and maintenance

Security and access control

- 13.1 Manufacturers should have systems and procedures in place to ensure data integrity and access control to computerized systems, and these measures should be commensurate with identified risks
- 13.2 Suitable security measures should be in place to prevent unauthorized entry or manipulation or deletion of data through the application software, as well as in operating system environments in which data may be stored or transmitted. Data should be entered or amended only by persons who are qualified and authorized to do so.
- 13.3 The activity of entering data, changing or amending incorrect entries, or creating backups should be done in accordance with SOPs.
- 13.4 Security should extend to devices used to store programs and data. Access to these devices should be controlled.
- 13.5 Measures for protecting audit trails from alteration or unauthorized deletion should be in place. Procedures for review of audit trails, and when necessary

metadata, should define the frequency, roles and responsibilities and nature of these reviews.

- 13.6 Operation of the system and acquisition of data should be traceable and should identify the persons who made entries and/or changes, approved decisions or performed other critical steps in system use or control.
- 13.7 Details of user profiles and access rights to systems, networks, servers, computerized systems and software should be documented and reviewed periodically. An up-to-date list on the individual user rights for the software, individual computer systems and networks should be maintained and subjected to change control. The level of detail should be sufficient to enable computer system validation personnel, as well as IT personnel/any external auditor/inspector, to ascertain that security features of the system and of software used to obtain and process critical data cannot be circumvented.
- 13.8 All GMP computerized systems, either stand-alone or in a network, should have a system that is commensurate with identified risks for monitoring through an audit trail of events that are relevant. These events should include all elements that need to be monitored to ensure that the integrity (1) of the data could not have been compromised without leaving a trace, such as, but not limited to, changes in or deletion of data; changes in dates, times, backups, archives or user access rights; and addition/deletion of users and log-ins, in accordance with WHO *Guidance on good data and record management practices* (1). The configuration and archiving of these audit trails should be documented and also be subjected to change control. These audit trails should be system generated, accurate, consistent, secure, available and convertible to a generally intelligible form throughout the retention period, and their generation appropriately qualified.

Operation and maintenance

- 13.9 Entry of GMP-related data into a computerized system should be verified by an independent authorized person and locked before release for routine use.
- 13.10 Validated computerized systems should be maintained in a validated state once released to the GMP production environment.
- 13.11 There should be written procedures governing system operation and maintenance, including, for example:
 - performance monitoring;
 - change management and configuration management;
 - problem/incident management;

- program and data security;
- program and data backup/restore and archiving/retrieval;
- system administration and maintenance;
- data flow and data life-cycle;
- system use and review of electronic data and metadata (such as audit trails);
- personnel training;
- disaster recovery and business continuity;
- availability of replacement parts and technical support;
- periodic re-evaluation.

13.12 Automatic or live updates should be subject to review prior to becoming effective.

Data migration

- 13.13 Where electronic data are transferred from one system to another, it should be demonstrated that data are not altered during the migration process. Conversion of data to a different format should be considered as data migration. Where data are transferred to another medium, they must be verified as an exact copy, prior to any destruction of the original data.
- 13.14 Procedures for data migration may vary greatly in complexity, and measures to ensure appropriate transfer of data should be commensurate with identified risks. Migrated data should remain usable and should retain their content and meaning. The value and/or meaning of and links between a system audit trail and electronic signatures should be ensured in a migration process.

Periodic review

- 13.15 Computerized systems should be periodically reviewed to determine whether the system remains in a validated state or whether there is a need for revalidation. The scope and extent of the revalidation should be determined using a risk-based approach. The review should at least cover:
- system performance and functionality;
 - security;
 - maintenance;
 - review of changes including upgrades;
 - review of deviations;
 - review of incidents/events (including review of audit trail);

- systems documentation;
- procedures;
- training;
- effectiveness of corrective and preventive action.

13.16 Corrective and preventive action should be taken where indicated as a result of the periodic review.

14. System retirement

- 14.1 System retirement should be considered as a system life-cycle phase. It should be planned, risk based and documented. If migration or archiving of GMP-relevant data (1, 2) is necessary, the process must be documented.
- 14.2 Once the computerized system or components are no longer needed, the system or components should be retired and decommissioned, in accordance with established authorized procedures, including a change-control procedure and a formal plan for retirement.
- 14.3 Records should be archived in a readable form and in a manner that preserves the accessibility, readability and integrity of the data of the source electronic records throughout the required records retention period.
- 14.4 The outcome of the retirement activities, including traceability of the data and computerized systems, as well as the ability to retrieve the data, should be tested and documented in a report.

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Appendix 6

Guidelines on qualification

Background

There was some confusion regarding the title of this appendix. It was therefore suggested to change the previous title *Validation on qualification of systems, utilities and equipment* to *Guidelines on qualification*. In this way, the general principles of qualification are addressed, which can be applied for systems, equipment, and so on.

Based on the comments, the general sections on objective and scope were written to make it clear that the guidelines address principles of qualification that can be applied, as appropriate, to premises, systems, utilities and equipment and to include the application of risk management principles.

Moreover, duplication was removed and logical flow of concepts addressed and aligned with international texts and the comments. Discussion of the V Model has been removed, based on the feedback received. In the former published text on qualification (see reference below), protocol formats were included. These protocol formats were extracted from training materials and were intended to serve as examples. In view of the feedback that manufacturers seemingly took them as absolute examples to be used, these examples have been removed in the current version.

This is a revision of the previous publication:

- Supplementary guidelines on good manufacturing practices: validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Appendix 6: Qualification of systems and equipment. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1).

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1. Principle

- 1.1 In principle, premises, systems, utilities and equipment should be appropriately designed, installed, qualified, operated, cleaned and maintained, to suit their intended purpose.
- 1.2 Quality management systems should be in place to ensure that these remain in a qualified state throughout their life-cycle.
- 1.3 Products should be produced and controlled using qualified equipment and instruments.
- 1.4 Manufacturers who may use an alternative verification framework to achieve qualification should ensure the qualification expectations within these guidelines are satisfied.

2. Scope

- 2.1 These guidelines describe the general approach to qualification of, for example, premises, systems, utilities and equipment.
- 2.2 The principles in these guidelines may also be applied to the qualification of instruments, analytical instruments and testing devices, where appropriate.
- 2.3 These may include, but are not limited to: certain rooms; water purification systems; cleaning systems; heating, ventilation and air-conditioning systems; compressed air systems; gas systems; and steam systems; as well as production equipment and analytical instruments.
- 2.4 Separate guidelines in this series address other principles in validation, such as process validation and cleaning validation (see Appendices 1–5 and 7).
- 2.5 The principle should be applied that a qualified state is maintained throughout the life-cycle.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

computerized system. A computerized system collectively controls the performance and execution of one or more automated processes and/or functions. It includes computer hardware, software, peripheral devices, networks and documentation, for example, manuals and standard operating procedures, as well as personnel interacting with hardware and software.

design qualification. Documented evidence that, for example, the premises, supporting systems, utilities and equipment have been designed for their intended purposes and in accordance with the requirements of good manufacturing practices.

factory acceptance test. A test conducted, usually at the vendor's premises, to verify that the system, equipment or utility, as assembled or partially assembled, meets approved specifications.

installation qualification. The performance of tests to ensure that the installations (such as machines, measuring devices, utilities and manufacturing areas) used in a manufacturing process are appropriately selected and correctly installed.

operational qualification. Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.

performance qualification. Documented verification that the equipment or system operates consistently and gives reproducibility within defined specifications and parameters, for prolonged periods.

site acceptance test. A test conducted at the manufacturer's site of use, to verify that the system, equipment or utility, as assembled or partially assembled, meets approved specifications.

user requirements specification. An authorized document that defines the requirements for use of the system, equipment or utility in its intended production environment.

utility. A system consisting of one or more components to form a structure designed to collectively operate, function or perform and provide a service, such as electricity, water, ventilation or other.

4. General

Note: The remainder of the text in these guidelines will refer to utilities and equipment as examples, even though the principles may be applicable to others such as premises and systems.

4.1 The validation master plan, or other relevant document, should specify the policy, organization, planning, scope and stages applied in qualification on site, and should cover, for example, production, quality control and engineering.

4.2 Principles of quality risk management should be applied in qualification. These include:

- a clear understanding of the system and the role it plays in establishing/protecting the process and quality, and all of the potential ways (risks) the process or quality could be impacted by failures, events, errors, or time/use-based factors (deterioration, out-of-tolerance instruments, wear and tear, and so on);

- defining all of the design, procedural and/or quality system controls required to protect against these potential risks. These controls either mitigate/reduce the risks and/or detect the impact to quality or process, should the risk occur (to ensure the “failure” does not impact final product quality);
 - compiling evidence during the design, engineering, commissioning and qualification, to demonstrate that all of these required “controls” have been properly implemented and verified (including “function” where applicable, such as alarms on operating parameters);
 - appropriate control and oversight of change once the controls have been verified.
- 4.3 The scope and extent of qualification and requalification should be determined based on the principles of impact assessment and risk management.
- 4.4 Qualification should be executed by trained personnel. Training records should be maintained.
- 4.5 Where appropriate, new premises, systems, utilities and equipment should be subjected to all stages of qualification. This includes the preparation of user requirements specification (URS), design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).
- 4.6 Where it is decided that not all stages of qualification are required, justification should be provided.
- 4.7 Qualification should be done in accordance with predetermined and approved qualification protocols. The protocol should specify the prerequisites and test details, including acceptance criteria.
- 4.8 The results of the qualification should be recorded and reflected in qualification reports.
- 4.9 A qualification report prepared at the completion of each protocol or stage of qualification (installation/operational/performance) should include, or reference as appropriate, the following:
- test results, including supporting calculations, documentation and raw/ original data;
 - test failures;
 - protocol departures;
 - recommendations and justification for issue resolution;
 - conclusions.

- 4.10 There should be a logical sequence for executing qualification, such as premises (rooms), then utilities and equipment.
- 4.11 Normally, qualification stages should be sequential (e.g. operational qualification should follow after the successful completion of installation qualification). In some cases, different stages of qualification may be executed concurrently. This should be justified and documented in the validation master plan (or qualification protocol).
- 4.12 Equipment should be released for routine use only once there is documented evidence that the qualification has been successful.
- 4.13 Certain stages of the qualification may be done by a supplier or a third party, subject to the conditions and responsibilities as defined in writing and agreed between the parties. The contract giver remains responsible to ensure that the qualification is done in accordance with the principles of good manufacturing practices.
- 4.14 The relevant documentation associated with qualification, including standard operating procedures, specifications and acceptance criteria, certificates and manuals, should be available.
- 4.15 Utilities and equipment should be maintained in a qualified state and should be periodically reviewed for the need for requalification. Requalification should be considered when changes are made.

5. User requirements specification

- 5.1 URS documentation should be prepared for, but not limited to, utilities and equipment, as appropriate.
- 5.2 URS should be used at later stages in qualification, to verify that the purchased and supplied utility or equipment is in accordance with the user's needs.

6. Design qualification

- 6.1 DQ should demonstrate that the system, as designed, is appropriate for its intended use as defined in the URS.
- 6.2 A suitable supplier should be selected and approved for the relevant utility or equipment.

7. Factory acceptance test and site acceptance test

- 7.1 Where a utility or equipment is assembled, or partially assembled at a site other than that of the purchaser or end-user, testing and verification may be done, based on principles of quality risk management, to ensure that it is appropriate, as described in the URS, and ready for dispatch.
- 7.2 The checks and tests conducted during the factory acceptance test (FAT) should be recorded.
- 7.3 The acceptability of the assembly and overall status of the utility or equipment should be described in a conclusion of the report for the FAT, prior to shipment.
- 7.4 Tests, based on principles of quality risk management, may be performed to verify the acceptability of the utility or equipment when it is received at the end-user. This is a site acceptance test (SAT).
- 7.5 The results of the tests should be evaluated and the outcome of the acceptability of the utility or equipment should be recorded in the conclusion section of the report for the SAT.

8. Installation qualification

- 8.1 Utilities and equipment should be correctly installed, in an appropriate location.
- 8.2 There should be documented evidence of the installation. This should be in accordance with the IQ protocol, which contains all the relevant details.
- 8.3 IQ should include identification and installation verification of relevant components identified (e.g. services, controls and gauges).
- 8.4 Identified measuring, control and indicating devices, should be calibrated on site, unless otherwise appropriately justified. The calibration should be traceable to national or international standards. Traceable certificates should be available.
- 8.5 Deviations and non-conformances, including those from URS, DQ and acceptance criteria specified and observed during installation, should be recorded, investigated and corrected or justified.
- 8.6 The outcome of the IQ should be recorded in the conclusion of the report, before OQ is started.

9. Operational qualification

- 9.1 Requirements and procedures for operation (or use), calibration, maintenance and cleaning should be prepared before OQ and approved prior to PQ.
- 9.2 Utilities and equipment should operate correctly and their operation should be verified in accordance with an OQ protocol. OQ normally follows IQ but, depending on the complexity of the utility or equipment, it may be performed as a combined installation/operation qualification (IOQ). This should be justified and documented in the validation master plan (or qualification protocol).
- 9.3 OQ should include, but is not limited to, the following:
 - tests that have been developed from the knowledge of processes, systems and equipment, to ensure the utility or equipment is operating as designed;
 - tests over the operating limits.
- 9.4 Training of operators for the utilities and equipment should be provided and training records maintained.
- 9.5 Calibration, cleaning, maintenance, training and related tests and results should be verified to be acceptable.
- 9.6 Deviations and non-conformances observed should be recorded, investigated and corrected or justified.
- 9.7 The results for the verification of operation should be documented in the OQ report.
- 9.8 The outcome of the OQ should be recorded in the conclusion of the report, normally before PQ is started.

10. Performance qualification

- 10.1 PQ should normally follow the successful completion of IQ and OQ. In some cases, it may be appropriate to perform PQ in conjunction with OQ or process validation. This should be justified and documented in the validation master plan (or qualification protocol).
- 10.2 PQ should include, but is not limited to, the following:
 - tests using production materials, qualified substitutes or simulated products proven to have equivalent behaviour under operating conditions, with batch sizes where appropriate;
 - tests covering the intended operating range.

- 10.3 Utilities and equipment should consistently perform in accordance with their design specifications and URS. The performance should be verified in accordance with a PQ protocol.
- 10.4 There should be records for the PQ (e.g. a PQ report), to indicate the satisfactory performance over a predefined period of time. Manufacturers should justify the period over which PQ is done.

11. Periodic review and requalification

- 11.1 Utilities and equipment should be maintained in a qualified state throughout the life-cycle of the utility or equipment.
- 11.2 Utilities and equipment should be reviewed periodically, to confirm that they remain in a qualified state or to determine the need for requalification.
- 11.3 Where the need for requalification is identified, this should be performed.
- 11.4 Principles of risk management should be applied in the review and requalification and the possible impact of small changes over a period of time should further be considered (such as, through change control).
- 11.5 Principles of risk management may include factors such as calibration, verification, maintenance data and other information.
- 11.6 The qualification status and periodic requalification due dates should be documented, for example, in a qualification matrix, schedule or plan.
- 11.7 In case a utility or equipment in use is identified that has not been subjected to qualification, a qualification protocol should be prepared where elements of URS, design specifications, operation and performance are verified for acceptability. The outcome of this qualification should be recorded in a report.

Appendix 7

Non sterile process validation

Background

The text of this appendix was previously published as:

- Guidelines on good manufacturing practices: validation. Appendix 7: Non-sterile process validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-ninth report. Geneva: World Health Organization; 2015: Annex 3 (WHO Technical Report Series, No. 992; https://iris.who.int/bitstream/handle/10665/176954/9789240693968_eng.pdf?sequence=1&isAllowed=y).

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1. Background and scope

Further to the *Supplementary guidelines on good manufacturing practices: validation*, as published in the World Health Organization (WHO) Technical Report Series (TRS), No. 937 (1), additional guidelines to support current approaches to good manufacturing practices (GMP) are published here. These guidelines are intended to further support the concept of process validation linked to principles of quality risk management and quality by design, as described by WHO and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

These guidelines allow for different approaches to process validation. The principles described are mainly applicable to non-sterile finished pharmaceutical dosage forms. Similar approaches may be applicable to active pharmaceutical ingredients (APIs) and sterile products. (See also recommendations in WHO TRS No. 957, Annex 2 (2) and WHO TRS No. 961, Annex 6 (3).)

A risk-based and life-cycle approach to validation is recommended.

Thorough knowledge of product and process development studies; previous manufacturing experience; and principles of quality risk management are essential in all approaches to process validation, as the focus is now on the life-cycle approach. The life-cycle approach links product and process development, validation of the commercial manufacturing process and maintaining the process in a state of control during routine commercial production. The use of process analytical technology, which may include in line, online and/or at-line controls and monitoring, is recommended, to ensure that a process is in a state of control during manufacture.

2. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

at-line. Measurement where the sample is removed, isolated from, and analysed in close proximity to the process stream.

concurrent validation. Validation carried out during routine production of products intended for sale in exceptional circumstances when data from replicate production runs are unavailable because only a limited number of batches have been produced, batches are produced infrequently or batches are produced by a validated process that has been modified. Individual batches may be evaluated and released before completion of the validation exercise, based on thorough monitoring and testing of the batches.

control strategy. A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to API and finished pharmaceutical product materials and components, facility and equipment operating

conditions, in-process controls, finished product specifications and the associated methods and frequency of monitoring and control.

continued process verification. Documented scientific evidence that the process remains in a state of control during commercial manufacture.

critical process parameter. A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored and/or controlled to ensure the process produces the desired quality.

critical quality attribute. A physical, chemical, biological or microbiological property or characteristic of materials or products that should be within an appropriate limit, range or distribution to ensure the desired product quality.

in-line. Measurement where the sample is not removed from the process stream; can be invasive or non-invasive.

life-cycle. All phases in the life of a product from the initial development through marketing until the product's discontinuation (4).

matrix approach or bracketing. Bracketing is the assessment of a single parameter or variable by identifying the edge(s) of the range of conditions for the parameter or variable and assessing these during validation, to span the possible range of that parameter or variable. For example, bracketing can be applied to process parameters, multiple pieces of identical equipment and/or different size considerations for the same product. The rationale for using this strategy should be justified, documented and approved.

Matrixing involves the assessment of the effect of more than one parameter or variable by using a multidimensional matrix to identify the “worst-case” or “extreme” conditions for a combination of parameters or variables. These conditions are used during validation of the process, rather than validating all possible combinations. Matrixing is typically used when there are significant similarities between products in a product family (e.g. the same product with different strengths in the manufacturing stage or different products with a similar container-closure in the packaging stage). The rationale for using this strategy should be justified, documented and approved.

The use of a matrix approach or bracketing design would not be considered appropriate if it is not possible to demonstrate that the extremes are limited to the batches, products, strengths, container sizes or fills. For those excluded from the exercise, there should be no risk to process capability.

online. Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.

pharmaceutical quality system. Management system to direct and control a pharmaceutical company with regard to quality.

process qualification. Process qualification combines the actual facility, utilities, equipment (each now qualified) and the trained personnel with the commercial manufacturing process, control procedures and components to produce commercial batches; confirms the process design; and demonstrates that the commercial manufacturing process performs as expected.

process validation. The collection and evaluation of data, from the process design stage through to commercial production, which establishes scientific evidence that a process is capable of continuously delivering the finished pharmaceutical product, meeting its predetermined specifications and quality attributes.

quality target product profile (QTPP). A prospectively documented summary of the quality characteristics of a finished pharmaceutical product (FPP) that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the FPP. The QTPP forms the basis of design for the development of the product and typically would include:

- intended use in a clinical setting, route of administration, dosage form, delivery systems;
- dosage strength(s);
- container-closure system;
- therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g. dissolution, aerodynamic performance) appropriate to the FPP dosage form being developed;
- FPP quality criteria (e.g. sterility, purity, stability and drug release) appropriate for the intended marketed product.

real-time release testing. The ability to evaluate and ensure the quality of in-process and/or final product, based on process data, which typically include a valid combination of measured material attributes and process controls.

state of control. A condition in which the set of controls consistently provides assurance of continued process performance and product quality.

3. Introduction

Process validation data should be generated for all products, to demonstrate the adequacy of the manufacturing process. The validation should be carried out in accordance with GMP and data should be held at the manufacturing location whenever possible and should be available for inspection.

Process validation is associated with the collection and evaluation of data throughout the life-cycle of a product – from the process design stage through to commercial production – and provides scientific evidence that a process is capable of consistently delivering a quality product. A risk-assessment approach should be followed, to determine the scope and extent to which process(es) and starting material variability may affect product quality. The critical steps and critical process parameters should be identified, justified and documented and based on relevant studies carried out during the design stage and on process knowledge, according to the stages of the product life-cycle. During process validation and qualification, the critical process parameters

should be monitored. It may be helpful to use a flow diagram depicting all the operations and controls in the process to be validated.

When applying quality risk management to a given operation, the steps preceding and following that operation should also be considered. Amendments to the flow diagram may be made where appropriate, and should be recorded as part of the validation documentation. Manufacturers should ensure that the principles of process validation described in these guidelines are implemented. These cover the phases of validation during process design; scale-up; qualification of premises, utilities and equipment; process performance qualification; and continuous process verification to ensure that the process remains in a state of control.

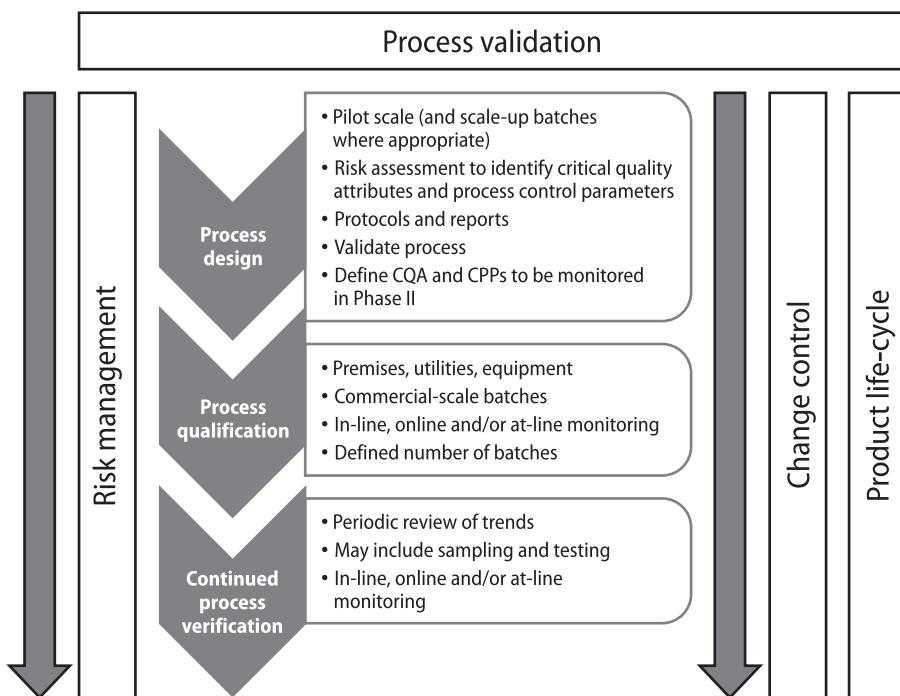
The objectives of process validation include ensuring that:

- the process design is evaluated to show that the process is reproducible, reliable and robust;
- the commercial manufacturing process is defined, monitored and controlled;
- assurance is gained on a continuous basis to show that the process remains in a state of control.

The validation should cover all manufactured strengths of a product, and the extent of validation at each manufacturing site should be based on risk assessment.

A matrix approach or bracketing may be acceptable and should also be based on appropriate risk assessment. There are various approaches to process validation, which include: traditional process validation (consisting of prospective and concurrent validation); process design followed by process qualification and continued process verification; or a combination of traditional process validation and the new approach described in these guidelines. Historical data should be evaluated in cases where there have been changes to the process. Manufacturers should plan to implement the new approach to process validation, which covers process design, process qualification and continued process verification throughout the product life-cycle. Fig. A3.7.1 shows the phases in the new approach to process validation.

Fig. A3.7.1
Phases of process validation



CQA: critical quality attribute; CPPs: critical process parameters.

4. Process design

Under the life-cycle approach, the focus of validation is shifted from commercial-scale batches to development. Product development activities provide key inputs to the process design stage, such as the intended dosage form, the quality attributes and a general manufacturing pathway. Laboratory or pilot-scale models designed to be representative of the commercial process can be used to estimate variability.

Process design should normally cover design of experiments, process development, the manufacture of products for use in clinical trials, pilot-scale batches and technology transfer. Process design should be verified during product development. Process design should cover aspects for the selection of materials; expected production variation; selection of production technology/process and qualification of the unitary processes that form the manufacturing process as a whole; selection of in-process controls; tests; inspection; and its suitability for the control strategy.

As part of the process validation life-cycle, some process validation studies may be conducted on pilot-scale batches (corresponding to at least 10% or 100 000 units,

whichever is the greater) of the production scale. Where the batch size is smaller and/or where the process is tailored to the geometry and capacity of specific equipment, it may be necessary to provide production-scale validation data.

Process qualification and continued process verification should always be linked to process design and be referenced to those specific batches used in studies critical to the development of the product, for example, the batch(es) used for pivotal clinical assessments (biobatch(es)), for example, bioequivalence testing in the case of multisource products, and toxicological studies. The number of batches included in the process design stage of validation should be appropriate and sufficient to include (but not be limited to) the expected variations in starting materials, and confirm the suitability of the equipment and manufacturing technology.

A statistically based design of experiment approach can be helpful during this stage. Processes and results should be appropriately documented. A development report and/or a technology transfer document, formally reviewed and approved by research and development personnel, and formally accepted by manufacturing, engineering and quality personnel, should be prepared. Such a document may include information such as a quality target product profile, desired clinical performance, bills of materials, approved suppliers, finished product specifications and test methods, in-process testing specifications, equipment recommendations, master batch production records, master batch packaging records, stability reports, critical quality attributes, critical process parameters, batch comparisons, data on formulation batches, stability batches, clinical/biobatches and scale-up batches. These documents should be readily available to the manufacturing site. The goal is to design a suitable process for routine commercial manufacturing that can consistently deliver a product that meets its required quality attributes.

5. Process qualification

Personnel, premises, utilities, support systems and equipment should be appropriately qualified before manufacturing processes are validated. Materials, environmental controls, measuring systems, apparatus and methods should be considered during validation. The stages of qualification of equipment may include design, installation, operation and performance of equipment (for more details see reference (1)).

Traditionally, three batches have been considered the normal and acceptable number for process validation; however, the number of batches should be justified and based on a risk assessment that includes, for example, variability of results from the process design stage, variability of materials, product history, where the product is being transferred from and where it will be produced. Manufacturers should define the stage at which the process is considered to be validated and the basis on which that decision was made. The decision should include a justification for the number of batches used based on the complexity and expected variability of the process and critical quality attributes (CQAs).

Successful completion of process performance qualification stage of the life-cycle is required for commercial distribution. A risk assessment should be performed for the change from scale-up to commercial batch size. Process qualification should confirm that scale-up in batch size did not adversely affect the characteristics of the product and that a process that operates within the predefined specified parameters consistently produces a product that meets all its CQAs and control strategy requirements. The process should be verified on commercial-scale batches prior to marketing of the product.

Extensive in-line and/or online and/or at-line controls may be used to monitor process performance and product quality in a timely manner. Results on relevant quality attributes of incoming materials or components, in-process material and finished products should be collected. This should include the verification of attributes, parameters and end-points and assessment of CQA and critical process parameter trends. Process analytical technology applications and multivariate statistical process control can be used. Manufacturers are encouraged to implement the new validation approach to ensure that processes are of known and acceptable capability. As full implementation of this approach may take time, the traditional approach of prospective validation and concurrent validation (used infrequently and restricted to the scenarios described in Section 3) may be acceptable in the interim. A combination of elements of the traditional process validation approach and the new continuous process verification approach may be considered appropriate, subject to appropriate controls being in place, based on scientific justification and principles of risk management.

Validation should be done in accordance with process validation protocols. A written protocol is essential for this stage of process validation. The protocol should include or reference at least the following elements:

- the manufacturing conditions, including operating parameters, processing limits and component (raw material) inputs;
- the data to be collected and when and how they will be evaluated;
- the type of testing or monitoring to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step;
- the scientifically justified sampling plan, including sampling points, number of samples and the frequency of sampling for each unit operation and attribute;
- the number of batches for which additional monitoring is proposed;
- status of the validation of analytical methods used in measuring the process, in-process materials and the product;
- a description of the statistical models or tools used;
- review and approval of the protocol by appropriate departments and the quality unit;
- a description of the process;

- details of the equipment and/or facilities to be used (including measuring or recording equipment) together with its calibration status;
- the variables to be monitored, with appropriate justification;
- the samples to be taken
- “who”, “where”, “when”, “how”, “how many” and “how much” (sample size);
- the product performance characteristics or attributes to be monitored, together with the test methods;
- the acceptable limits;
- personnel responsibilities;
- details of methods for recording and evaluating results, including statistical analysis. Data should be collected and reviewed against predetermined acceptance criteria and fully documented in process validation reports.

The report should reflect the validation protocol. A dual protocol report can be used; however, such reports must be designed to ensure clarity and sufficient space for recording of results. The outcome should confirm that the acceptance criteria have been met. Any deviations (including abandoned studies) should be explained and justified. The planned commercial production and control records, which contain the operational limits and overall strategy for process control, should be carried forward to the next phase for confirmation.

6. Continued process verification

Manufacturers should monitor the product quality of commercial batches after completion of process design and process qualification. This will provide evidence that a state of control is maintained throughout the product life-cycle.

The scope and extent of process verification will be influenced by a number of factors, including:

- prior development and knowledge of the manufacturing of similar products and/or processes;
- the extent of process understanding gained from development studies and commercial manufacturing experience;
- the complexity of the product and/or manufacturing process;
- the level of process automation and analytical technologies used;
- for legacy products, with reference to the product life-cycle process, robustness and manufacturing history since the point of commercialization, as appropriate.

Manufacturers should describe the appropriateness and feasibility of the verification strategy (in the protocol), including the process parameters and material attributes that will be monitored, as well as the validated analytical methods that will be employed.

Manufacturers should define:

- the type of testing or monitoring to be performed;
- the acceptance criteria to be applied;
- how the data will be evaluated and the actions to be taken.

Any statistical models or tools used should be described. If continuous processing is employed, the stage at which the commercial process is considered to be validated should be stated, based on the complexity of the process, expected variability and manufacturing experience of the company. Periods of enhanced sampling and monitoring may help to increase process understanding as part of continuous improvement. Information on process trends, such as the quality of incoming materials or components, in process and finished product results and non-conformances, should be collected and assessed to verify the validity of the original process validation or to identify changes to the control strategy required. The scope of continued process verification should be reviewed periodically, and modified if appropriate, throughout the product life-cycle.

7. Change management

Manufacturers should follow change-control procedures when changes are planned to existing systems or processes. The change-control procedure and records should ensure that all aspects are thoroughly documented and approved, including regulatory approval where appropriate (variation).

Sufficient data should be generated to demonstrate that the revised process will result in a product of the desired quality, consistent with approved specifications.

Validation should be considered when changes to production and/or control procedures are planned. Based on risk assessment, changes that may require revalidation could include (but are not limited to):

- changes in the master formula, methods, starting material manufacturer, starting material manufacturing process, excipient manufacturer, excipient manufacturing process;
- changes in the equipment or instruments (e.g. addition of automatic detection systems);
- changes associated with equipment calibrations and the preventive maintenance carried out, which may impact the process;

- production area and support system changes (e.g. rearrangement of areas or a new water-treatment method);
- changes in the manufacturing process (e.g. mixing times, drying temperatures);
- transfer of processes to another site;
- unexpected changes (e.g. those observed during self-inspection or during routine analysis of process trend data);
- changes to standard operating procedures;
- changes to cleaning and hygiene programmes.

Depending upon the nature of the change being proposed, the change-control process should consider whether existing approved specifications will be adequate to control the product subsequent to implementation of the change.

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Further reading

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1.3 Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation

Annex 2, WHO Technical Report Series, 1033, 2021 (new)

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1. Introduction and background

The World Health Organization (WHO) has published the guideline entitled *Good manufacturing practices for pharmaceutical products: main principles* in the WHO Technical Report Series, No. 986, Annex 2, 2014 (1).

The WHO *Supplementary guidelines on good manufacturing practice: validation* were published in 2006 and were supported by seven appendices. The main text (2) and its appendixes (3, 4, 6, 7, 8, 9) were revised between 2006 and 2019. Appendix 3, relating to cleaning validation (5), was not updated at that time. Its revision, however, was discussed during an informal consultation held in Geneva, Switzerland, in July 2019. The outcome of the discussion was presented to the WHO Expert Committee on Specifications for Pharmaceutical Products (ECSPP) meeting in October 2019. The ECSPP acknowledged the importance of harmonization in regulatory expectations with regards to cleaning validation approaches. The Expert Committee recommended a “Points to consider” document be prepared in order to describe the current approaches used in cleaning validation and highlighting the complexities involved in order to establish a common understanding. A revision of the relevant appendix would then be considered by the Expert Committee thereafter.

Some of the main principles of good manufacturing practices (GMP) include the prevention of mix-ups and the prevention of contamination and cross-contamination. Multi-product facilities in particular, have a potential risk of cross-contamination. It is therefore important that manufacturers identify all risks relating to contamination and cross-contamination and identify and implement the appropriate controls to mitigate these risks.

These controls may include, for example, technical and organizational measures, dedicated facilities, closed systems, cleaning and cleaning validation.

It is strongly recommended that manufacturers review their existing technical and organizational measures, suitability of cleaning procedures and appropriateness of existing cleaning validation studies.

Technical controls, such as the design of the premises and utilities (e.g. heating, ventilation and air-conditioning [HVAC], water and gas), should be appropriate for the range of products manufactured (e.g. pharmacological classification, activities and properties). Effective controls should be implemented to prevent cross-contamination when air is re-circulated through the HVAC system.

Organizational controls, such as dedicated areas and utilities, dedicated equipment, procedural control, and campaign production, should be considered where appropriate as a means to reduce the risk of cross-contamination.

Measures to prevent cross-contamination and their effectiveness should be reviewed periodically in accordance with authorized procedures.

It should be noted that the above examples are described in more detail in other documents. The focus of this document is on Health-Based Exposure Limits (HBELs) setting in cleaning validation.

2. Scope

This document provides points to consider for a risk and science-based approach when considering HBELs, based on pharmacological and toxicological data, in cleaning validation.

This document further provides points to consider when reviewing the current status and approaches to cleaning validation in multiproduct facilities.

The principles described in this document may be applied in facilities where active pharmaceutical ingredients (APIs), investigational medical products (IMP), vaccines, human and veterinary medical products are manufactured. The principles may also be considered, where appropriate, in facilities where medical devices are manufactured.

This document should be read in conjunction with the main GMP text and supplementary texts on validation (1–9).

3. Glossary

Adjustment factor (safety factors). Numerical factor used in a quantitative risk assessment to represent or allow for the extrapolation, uncertainty, or variability of an observed exposure concentration and its associated health outcome in a particular laboratory species or exposed population to an exposure concentration for the target population (for example, from animals to human patients and short-term exposure to chronic exposure) that would be associated with the same delivered dose. Adjustment factors can also be used when dealing with clinical data, e.g. when a study population is not representative of the general population (10).

Cleanability. The ability of a cleaning procedure to effectively remove material, cleaning agent residue and microbial contamination.

Cleaning validation. The collection and evaluation of data, from the cleaning process design stage through cleaning at commercial scale, which establishes scientific evidence that a cleaning process is capable of consistently delivering clean equipment, taking into consideration factors such as batch size, dosing, toxicology and equipment size.

Contamination. The presence of undesired foreign entities of a chemical, microbiological or physical nature in or on equipment, a starting material, or an intermediate or pharmaceutical product during handling, production, sampling, packaging, repackaging, storage or transport.

Cross-contamination. Contamination of a starting material, intermediate product or finished product with another starting material or product.

Health Based Exposure Limits (HBELs). See definition of *Permitted Daily Exposure (PDE)*

Margin of safety. The margin of safety is the ratio between the cleaning acceptance limit based on HBEL and the process residue data.

Maximum safe carryover (MSC). The maximum amount of carryover of a residual process residue (API, cleaning agent, degradant, and so forth) into the next product manufactured without presenting an appreciable health risk to patients.

Maximum safe surface residue (MSSR). The MSSR is the maximum amount of process residue that can remain on equipment surfaces and still be safe to patients. The MSSR is mathematically calculated by dividing the Maximum Safe Carryover (MSC) by the total area of shared contact (MSC/Total Product Contact Surface Area).

Permitted daily exposure (PDE). PDE represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime.

Point of departure (of the HBEL calculation). The dose-response point that marks the beginning of a low-dose extrapolation to derive an HBEL. This point can be a No Observed Adverse Effect Level (NOAEL) or No Observed Effect Level (NOEL), Lowest Observed Adverse Effect Level (LOAEL) or Lowest Observed Effect Level (LOEL), or Benchmark Dose Level (BMDL) for an observed effect [the highest dose at which no unwanted/adverse effect is observed (NOEL/NOAEL), or, if unavailable, the dose at which a significant adverse effect is first observed (LOEL/LOAEL)].

Verification. Evidence that the equipment is clean (i.e. that residues are reduced from prior operations to levels no higher than those that are predetermined and specified as acceptable). Appropriate methods should be used and, depending upon the circumstances, may include visual inspection, analytical and microbial (as applicable) testing of swab and/or rinse samples.

4. Historical approach in cleaning validation

For details on the historical approaches in cleaning validation, see the WHO Technical Report Series, No. 1019, Annexure 3, Appendix 3, 2019 (5).

The acceptance criteria for cleaning validation recommended in historical GMP texts did not account for HBELs. A cleaning limit based on HBELs should be calculated and compared against an existing cleaning limit. Historically established cleaning limits may be used when these are more stringent than HBELs. Any alert and action limits should not be based on historically established cleaning limits, but should be based on a statistical analysis if existing data (i.e. statistical process control).

Where the historical approach cannot be satisfactorily justified, and in view of the risks of contamination and cross-contamination, the new approaches, as described below, should be prioritized and implemented.

5. New approach using HBELs in cleaning validation

Historical cleaning validation approaches often merely showed that using a defined cleaning procedure achieved an objective of meeting historical limits. In many instances, no development work or cleanability studies were done nor was consideration given to pharmacological and toxicological data for establishing limits for cleaning residues.

Manufacturers should ensure that their cleaning procedures are appropriately developed and that their cleaning validation provides scientific evidence that residues of identified products that can be manufactured in shared facilities are removed to levels considered as safe for patients. Control measures should be implemented to mitigate the risks of contamination and cross-contamination.

This approach should include at least the following points (some of which are further described in the text below):

risk assessment to identify cross-contamination hazards, analyse risks, and to identify risk controls;

- cleaning procedure development studies including cleanability studies, where applicable (e.g. new products or cleaning procedures);
- determination of technical and organizational controls;
- HBELs setting;
- selection of appropriate analytical procedures; and
- cleaning process control strategy.

Manufacturers should describe and implement their policy and approaches, including the points mentioned above, in a document such as a master plan.

Genotoxic and carcinogenic substances, degradants and other contaminants (if relevant) should be identified and their risks evaluated. Appropriate action should be taken where required (11).

5.1 Documentation

Risk management principles, as described by WHO and other guidelines on quality risk management (12), should be applied to assist in identifying and assessing risks. The appropriate controls should be identified and implemented to mitigate contamination and cross-contamination.

The policy and approaches in cleaning and cleaning validation require that good scientific practices should be applied (including the use of appropriate equipment and

methods). This should be described in a cleaning validation master plan. Development studies, cleaning and cleaning validation should be performed in accordance with predefined, authorized standard operating procedures, protocols and reports, as appropriate. Records should be maintained and available.

The design and layout of documents, and the reporting of data and information, should be in compliance with the principles of good documentation practices (13) and should also meet data integrity requirements (14).

5.2 Equipment

Cleaning validation should cover direct product contact surfaces. Non-contact surfaces should be included in cleaning validation where these have been identified as areas of risk.

Authorized drawings of equipment should be current, accurate and available. Equipment surface area calculations should be documented and justified. The source data for these calculations should be available. The calculated values should be used in the calculations in cleaning validation.

All shared equipment and components, including those that are difficult to clean (for example sieves, screens, filters and bags [such as centrifuge bags]) should be considered in cleaning validation and calculations.

Where the need is identified, dedicated equipment and or components should be used.

5.3 Cleaning agents

Cleaning agents (including solvents and detergents used in cleaning processes) should be selected based on cleaning process development studies including cleanability studies. They should be appropriate for their intended use.

There should be proof of effectiveness and appropriateness of the selected cleaning agent.

Other points to consider include the concentration in which these are used, their composition and removal of their residues to an acceptable level.

5.4 Sampling

Historically, cleaning validation has focused mainly on product contact surface areas.

A combination of at least two or three methods should normally be used. These include swab samples, rinse samples and visual inspection. Visual inspection should always be performed where possible and safe to do so. Sampling should be carried out by swabbing whenever possible. Rinse samples should be taken for areas which are inaccessible for swab sampling. The sampling materials and method should not influence the result.

Appropriate sampling procedures, swab material and sampling techniques should be selected and used to collect swab and rinse samples. The detail should be

clearly described in procedures and protocols. The number of swabs, location of swabbing, swab area, rinse sample volume and the manner in which the samples are collected should be scientifically justified.

Swab and rinse sample methods should be validated for commercial product manufacturing and verified for IMPs. Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used.

Where microbiological sampling is carried out, a compendial or validated method should be used.

The manner in which collected samples are stored (if required) and prepared for analysis should be appropriate, described in detail and included in the cleaning validation.

5.5 Cleanability studies

Before a new cleaning procedure is validated and adopted for routine use, a cleanability study should be performed in order to determine the appropriateness of the procedure for removing for example product residue, cleaning agents and microorganisms. For cleaning procedures that have already been validated where the data show that the cleaning procedure is effective and consistent, or where risk assessment indicated that cleanability studies may not be required, this may be considered acceptable.

5.6 Risk management

Risk management should be implemented with a focus on the identification, evaluation, assessment and control of risks to mitigate the risk of contamination and cross-contamination.

Measures should include technical and organizational controls in order to deliver a verified or validated cleaning process (12).

5.7 Guidance for Health-Based Exposure Limits (HBELs) setting

Manufacturers should establish, document and implement a company-wide policy on HBELs setting for shared facilities.

The appropriateness of the production and control of various APIs or various products in shared facilities should be evaluated on the basis of scientific data and information.

This is applicable to products already produced in a facility as well as when new products are planned to be introduced into a facility, for example, through a change control procedure.

Procedures should be established and implemented describing how the scientific and toxicological data and information are obtained and considered and how HBELs are established.

Data and information should be gathered and critically evaluated by a qualified expert. A qualified expert is an individual with relevant qualifications including educational background (e.g. toxicology, pharmacology or related health fields), certifications (e.g. (e.g. Diplomate of the American Board of Toxicology (DABT), European Registered Toxicologist (ERT) and with adequate experience in the practice of deriving HBELs, such as occupational exposure limits (OELs), PDEs for residual solvents, elemental impurities, and product contamination/nonconformances. The data and evaluation should be presented in a report that is peer-reviewed by another qualified expert (10, 15). The data and information presented should be free from bias.

Where this service is outsourced by the manufacturer, appropriate measures should be put in place in order to ensure that the data obtained are reliable. GMP requirements, such as vendor qualification, agreements and other related aspects, should be considered.

Note: The HBEL value for the same substance sometimes differs when it is determined by different individuals. The reason for the difference between the values should be clarified and investigated.

The report for each substance should include scientific detail and information, as applicable, such as:

- substance identification
- chemical structure
- clinical indication
- mode of action
- route of administration (*Note: Where there is more than one route of administration, separate HBELs should be derived for each route*)
- preclinical/nonclinical data, for example, of acute and repeat-dose toxicity data
 - genotoxicity data
 - carcinogenicity data
 - reproductive and developmental toxicity data
 - immunotoxicity and sensitization data
- clinical data
- pharmacodynamics and pharmacokinetics
- identification of the critical effect(s)
- point of departure for the HBEL calculation(s)
- adjustment factors
- justification of the selected lead rationale (if calculations with different points of departure were made).

The report should be reviewed for its completeness and appropriateness by the manufacturer's designated internal personnel or by an appointed external person. The person should have in-depth knowledge, appropriate qualifications and experience (see above). A summary document may be prepared from the report, for each relevant substance, which contains the key pharmacological/toxicological characteristics of the compound, the effect that drives the HBEL ("lead effect"), the basis of the rationale that has been used to set the HBEL and the HBEL itself including the route/s of exposure for which the HBEL(s) is/are valid (15, 16, 17, 18, 19).

The scientific report and calculated PDE value should be used when defining the limits used in cleaning validation.

Note: If no NOAEL is obtained, the LOAEL may be used. Alternative approaches to the NOAEL, such as the benchmark dose, may also be used. The use of other approaches to determine HBELs could be considered acceptable if adequately and scientifically justified (16, 17).

Manufacturers should periodically consider new data and information on HBELs. Appropriate action, such as the updating of PDE reports, should be taken where required.

Note: therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. The cleaning of biopharmaceutical manufacturing equipment is typically performed under conditions which expose equipment surfaces to pH extremes and/or heat, which would lead to the degradation and inactivation of protein-based products. In view of this, the determination of health-based exposure limits using PDE limits of the active and intact product may not be required.

Where other potential routes of cross-contamination exist, the risks posed should be considered on a case-by-case basis.

5.8 Acceptance criteria

The limits established in cleaning validation should be scientifically justified.

Historically, some manufacturers have specified acceptance criteria where HBELs and related toxicity data were not included in the determination of such acceptance criteria.

Criteria such as Maximum Safe Carryover (MSC) and Maximum Safe Surface Residue (MSSR) values should be calculated. Calculations and data should be available and comply with data integrity principles. The calculation should include values of PDE, maximum daily dose, batch size and total shared equipment surface areas, sample areas, sample dilution volumes and recovery factors.

MSC and MSSR should be calculated and presented, for example, in table form listing preceding and following product values. The cleanability value obtained should be considered in determining the acceptability of the procedure(s) and whether other

controls including separate, dedicated facilities are required (*for example of IMPs see EudraLex Volume 4 Part 1 Chapter 3.6, Annex 15, Annex 13*).

The margin of safety should be identified.

5.9 Analytical procedures

Samples obtained in cleaning validation should be analyzed by using procedures that are validated for their intended use. The procedures should be developed in accordance with the principles of Analytical Quality by Design.

Specific methods, such as High-performance Liquid Chromatography (HPLC), should be used where appropriate. UV spectrophotometric methods and testing for total organic carbon (TOC) may be used where indicated and where justified. Non-specific methods should only be used where specific methods cannot be employed and their use can be justified, for example, based on the outcome of risk assessment.

Where analytical procedures were developed and validated off-site, the scope and extent of validation when these are transferred to the site, should be defined and justified. This includes procedures that are transferred from research and development laboratories to site laboratories. Analytical procedures should be able to quantify residue levels at the maximum safe surface residue level. (For analytical procedure validation, see reference 6.)

Manufacturers should ensure that the procedures remain in a validated state.

5.10 Data integrity

Data, information and results pertaining to, for example, HBELs, PDE reports, results obtained from cleaning validation and calculations, should be scientific and should be in compliance with the principles as contained in data integrity guidelines (14).

5.11 Cleaning validation and cleaning verification

Cleaning validation

The cleaning procedure should be validated (5).

Cleaning validation should include proof of, for example, the applicability of the procedure to clean equipment that:

- had been kept in an unclean state for a period of time (dirty equipment hold time);
- are used after a product is planned (e.g. change from one product to another product);
- are used in a campaign, where multiple batches of a product are produced one after the other; and/or
- are stored in a clean state for defined periods of time (clean equipment hold time).

HBELs should be considered when establishing carryover limits in cleaning validation.

Cleaning verification

The company should describe the policy and approach to cleaning verification. Cleaning verification is where the effectiveness of the validated cleaning procedure is routinely verified. The approach may include swab or rinse samples and should include the same sampling and testing procedures used in cleaning validation. The results obtained from testing on a routine basis should be reviewed and subjected to statistical trending if possible.

5.12 Visually clean

Visually clean is an important criterion in cleaning validation. It should be one of the acceptance criteria used on a routine basis. Personnel responsible for visual inspection should be appropriately trained and qualified and training records should be kept.

Where visual inspection is used as a quantitative method, then Visible Residue Limits (VRLs) should be determined. The process to determine the limit should be appropriately described in procedures and protocols covering, for example, concentrations, method of spiking, surface areas, material of construction and other conditions such as light (LUX level) and angles. The acceptability of visual inspection should be determined by comparing the VRL of that compound to the MSSR with an appropriate safety margin.

5.13 Cleaning process capability

The cleaning procedure should remain in a validated state. It is recommended that Process Capability (C_{pk}) be calculated and Statistical Process Control (SPC) be used to support cleaning verification results and data. For example, the results from cleaning verification sample analysis could be statistically trended. The capability (C_{pk}) of the cleaning process is then calculated using an appropriate statistical technique.

Data should be presented, for example, in graph form, and the capability of the process in relation to control limits and the margin of safety should be presented and discussed as part of continuous improvement over the life cycle.

5.14 Personnel

Personnel should be trained on the procedures and principles of cleaning and cleaning validation, including contamination and cross-contamination control, HBELs setting, equipment disassembly, visual inspection, sampling, testing and statistical calculations, as appropriate and based on their responsibilities.

5.15 Life cycle

Cleaning procedures, cleaning validation and cleaning verification should be included in the life cycle approach described by the company.

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Appendix 1

Using Health-Based Exposure Limits (HBELs) to assess risk in cleaning validation*

Permitted Daily Exposure (PDE)

The Permitted Daily Exposure (PDE) can be calculated based on the data and information obtained. For example:

$$\text{PDE} = \frac{\text{NOAEL} \times \text{weight adjustment}}{\text{F1} \times \text{F2} \times \text{F3} \times \text{F4} \times \text{F5}}$$

Where NOAEL is no-observed adverse effect level, and

F represents various adjustment factors. The value selected for each factor should be justified. All adjustment factors should ideally be compound-specific. Default values should only be used where no compound-specific data are available.

The PDE is derived by dividing the NOAEL for the critical effect by various adjustment factors (also referred to as safety-, uncertainty-, assessment- or modifying factors) to account for various uncertainties and to allow extrapolation to a reliable and robust no-effect level in the human or target animal population. (*Note: The values for the factors cited below are defaults and should only be used in the absence of compound-specific information*).

F1 to F5 are addressing the following sources of uncertainty:

- F1: A factor (values between 2 and 12) to account for extrapolation between species;
- F2: A factor of 10 to account for variability between individuals;
- F3: A factor 10 to account for repeat-dose toxicity studies of short duration, i.e., less than 4-weeks;
- F4: A factor (1-10) that may be applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity;
- F5: A variable factor that may be applied if the no-effect level was not established. When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

* Barle, E.L. Using Health-Based Exposure Limits to assess risk in cleaning validation. Pharmaceutical Technology

The use of additional modifying factors to address residual uncertainties not covered by the above factors may be accepted provided they are well supported with literature data and an adequate discussion is provided to support their use (17).

If no NOAEL is obtained, the lowest-observed-adverse-effect level (LOAEL) may be used.

Calculating Maximum Safe Carryover (MSC) and Maximum Safe Surface Residue (MSSR)

MSC and MSSR can be calculated by using HBELs, to determine the risks associated with cleaning validation.

Step 1. Calculate MSC:

$$\text{MSC a (g)} = \frac{\text{PDE a (ug)} \times \text{Batch size b (kg)}}{\text{Maximum Daily Dose b (mg)}}$$

Where a = product a

b = product b or subsequent product

Step 2. Tabulate the data

API	PDE ug/day	MDD mg/day	Batch size Kg	Shared Equipment surface (m ²)
1				
2				
3				
4				
5				

Step 3. Calculate MSSR (mg/m²)

$$\text{MSSR} = \frac{\text{MSC a (g)} \times 1000}{\text{Shared surface for b (m}^2\text{)}}$$

Step 4. Tabulate the data for MSSR and identify where there is a risk, based on the MSSR that are not met when considering the cleanability of the procedure or the Visual Residue Limit of the compound / product.

MSSR		Following product b					
		1	2	3	4	5	6
Pre-Cleaning Product a	1						
	2						
	3						
	4						
	5						
	6						

1.4 Good manufacturing practices: water for pharmaceutical use

Annex 3, WHO Technical Report Series, 1033, 2021 (revised)

Background

Unlike other product or process ingredients, water is usually drawn from an on-demand system and is not subject to testing and batch or lot release prior to use. Thus it is essential that water quality (including microbiological and chemical quality) throughout production, storage and distribution processes is controlled.

In recent years, following extensive consultations with stakeholders, several pharmacopoeias have adopted revised monographs on water for injection (WFI) that allow for production by non-distillation technologies. In 2017, the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) recommended that the WHO Secretariat collect feedback on whether or not they should revise the WHO specifications and good manufacturing practices (GMP) on WFI and, if so, how to do so. Following several consultations, the ECSPP agreed that the monograph in *The International Pharmacopoeia (Water for injections)* and the guideline *WHO Good manufacturing practices: water for pharmaceutical use* (1), should both be revised to allow for technologies other than distillation for the production of WFI.

In early 2019, the WHO Secretariat commissioned a draft guidance text for the production of WFI by means other than distillation. Following several public consultations, the text was presented to the Fifty-fourth ECSPP. The Expert Committee adopted the *Production of water for injection by means other than distillation* guideline and recommended that it should also be integrated into WHO's existing guideline on *Good manufacturing practices: water for pharmaceutical use*.

This document is a revision of *WHO Good manufacturing practices: water for pharmaceutical use*, previously published in the WHO Technical Report Series, No. 970, Annex 2, 2011.

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1. Introduction and scope

- 1.1 This document concerns water for pharmaceutical use (WPU) produced, stored and distributed in bulk form. It provides information on different specifications for WPU; good practices for the management of the quality of water systems; water treatment (production) systems; water storage and distribution systems; commissioning, qualification and validation; sampling and testing; and the routine monitoring of water.
- 1.2 The focus of this document is on the treatment, storage and distribution of treated water used in pharmaceutical applications. It excludes the production, storage and usage of water in quality-control laboratories.
- 1.3 This document does not cover water for administration to patients in the formulated state or the use of small quantities of water in pharmacies to compound individually prescribed medicines.
- 1.4 The document can be used in whole or in part, as appropriate, to the section and application under consideration.
- 1.5 In addition to this document, the “Further reading” section at the end of this document includes publications that can serve as additional background material when planning, installing and operating systems intended to provide WPU.
- 1.6 This document is supplementary to the *WHO good manufacturing practices for active pharmaceutical ingredients* (2), and the *WHO good manufacturing practices for pharmaceutical products: main principles* (3).

2. Background to water requirements and uses

- 2.1 Water is a widely used substance in the pharmaceutical industry and other sectors involved in manufacturing pharmaceutical products. It is extensively used as a raw material or starting material in the production, processing and formulation of active pharmaceutical ingredients (APIs), intermediates and finished pharmaceutical products (FPP), in the preparation of solvents and reagents, and for cleaning (e.g. washing and rinsing). Water has unique chemical properties due to its polarity and hydrogen bonds. These include a relatively high boiling point, high specific heat, cohesion, adhesion and density. These include contaminants that may be hazards in themselves or that may be able to react with product substances, resulting in hazards to health. Water should therefore meet appropriate quality standards to mitigate these risks.

- 2.2 The microbiological and chemical quality of water should be controlled throughout production, storage and distribution. While chemical test results can normally be obtained without delay, results from microbiological testing are normally available only after water has already been used as microbiological tests may require periods of incubation. The assurance of quality to meet the on-demand expectation of water is therefore essential.
- 2.3 To reduce the risks associated with the production, storage and distribution of water, and considering the properties and use, it is essential:
 - to ensure the appropriate design, installation, operation and maintenance of WPU, pre-treatment, treatment, storage and distribution systems;
 - to continuously or periodically perform sanitization;
 - to take the appropriate measures in order to minimize chemical and microbial contamination; and
 - to minimize microbial proliferation and endotoxin formation, where applicable.
- 2.4 Different grades of water quality exist. The appropriate water quality, meeting its defined specification (such as described in a pharmacopoeia), should be used for the intended application.
- 2.5 The application of specific types of water to processes and dosage forms should be considered.
- 2.6 Pharmaceutical manufacturers should use the appropriate grade of WPU during, for example, the manufacture of APIs and different dosage forms, for different stages in washing and cleaning, and in the synthesis of materials and products.
- 2.7 The grade of water used should take into account the nature and intended use of the intermediate or FPP and the stage in the manufacturing process at which the water is used.
- 2.8 Bulk water for injections (BWFI) should be used, for example, in the manufacture of injectable products, such as dissolving or diluting substances or preparations during the manufacturing of parenteral products, and for the manufacture of water for preparation of injections. BWFI should also be used for the final rinse after the cleaning of equipment and components that come into contact with injectable products, as well as for the final rinse in a washing process in which no subsequent thermal or chemical depyrogenization process is applied.

3. General principles for pharmaceutical water systems

- 3.1 Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, qualified, validated, operated and maintained to ensure the consistent and reliable production of water of appropriate quality.
- 3.2 The capacity of these systems should be enough to meet both the minimum and peak demand. These systems should be able to operate continuously for significant periods of time in order to avoid the inefficiencies and equipment stresses that occur when equipment cycles turn on and off too frequently.
- 3.3 Qualification may include stages such as preparing User Requirement Specifications (URS), Factory Acceptance Tests (FAT), Site Acceptance Tests (SAT), as well as installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). The release and use of the system should be approved by the quality unit, e.g. quality assurance (QA) at an appropriate stage of qualification and validation (see section 11 below).
- 3.4 Water sources and treated water should be monitored regularly for chemical, microbiological and, where appropriate, endotoxin contamination. The performance of water treatment, storage and distribution systems should also be monitored. Records of the results monitored, trend analysis and any actions taken should be maintained.

4. Water quality specifications

4.1 Pharmacopoeial specifications

- 4.1.1 Pharmacopoeias include specifications for water used in bulk and in dosage forms. Where this document refers to specifications, such as those in pharmacopoeias, the relevant, current publications should be used. This document does not attempt to duplicate such material. Where subtle points of difference exist between pharmacopoeial specifications, the manufacturer should choose the appropriate specification in accordance with the related marketing authorization submitted to the relevant medicine's regulatory authority. Pharmacopoeial requirements or guidance for WPU are described in national, regional and international pharmacopoeias (4) and limits for various impurities, or classes of impurities, are either specified or recommended. Requirements or guidance are given in pharmacopoeias on the microbiological and chemical quality of water.

4.2 Drinking-water

Note: The requirements for the design, construction and commissioning of drinking water systems are usually controlled through local regulations. Drinking water systems are not usually qualified or validated, but subjected to commissioning.¹

- 4.2.1 The quality of drinking-water is covered by the *WHO guidelines for drinking-water quality* (5) and standards from the International Organization for Standardization (ISO) and other regional and national agencies. Drinking-water should comply with the relevant regulations laid down by the relevant authority.
- 4.2.2 Drinking-water may be derived from a natural or stored source. Examples of natural sources include springs, wells, rivers, lakes and seas. The condition of the source water should be considered when choosing a treatment to produce drinking-water.
- 4.2.3 Drinking-water should be supplied under continuous positive pressure by a plumbing system free from any defects that could lead to contamination.
- 4.2.4 Drinking-water may be derived from a public water supply system. This includes an off-site source, such as a municipality. Appropriate drinking-water quality should be ensured by the supplier. Tests should be conducted to guarantee that the drinking-water delivered is of drinking quality. This testing is typically performed on water when taken from the water source. Where required, quality may be achieved through processing on-site.
- 4.2.5 Where drinking-water is purchased in bulk and transported to the user by water tankers, controls should be put into place to mitigate any associated risks. Vendor assessment and authorized certification activities, including confirmation of the acceptability of the delivery vehicle, should be undertaken in a similar way to that used for any other starting material.
- 4.2.6 It is the responsibility of the pharmaceutical manufacturer to assure that the source water supplying the purified water (PW) treatment system meets the appropriate drinking-water requirements. In these situations, the point at which drinking-water quality is achieved should be identified and a water sample taken and tested at defined intervals thereafter.
- 4.2.7 If drinking-water is used directly in certain stages of pharmaceutical manufacture, such as in the production of APIs or in the feedwater for the production of higher qualities of WPU, then testing should be carried out periodically by the water

¹ See documents listed under Further reading.

user's site; for example, at the point of use, to confirm that the quality meets the standards required for drinking-water. The selection of tests to be performed, and the frequency of testing, should be based on a risk assessment.

- 4.2.8 Where drinking-water is produced through the treatment of raw water by a system on-site, the system configuration and water-treatment steps used should be described.
- 4.2.9 Examples of typical processes employed to produce drinking-water may include:
 - desalination;
 - filtration;
 - softening;
 - disinfection or sanitization, such as by ozone or sodium hypochlorite (chlorine);
 - iron (ferrous) removal;
 - precipitation; and
 - the reduction of concentration of specific inorganic and/or organic materials.
- 4.2.10 Controls should be implemented to minimize the microbiological contamination of sand filters, carbon beds and water softeners. The techniques selected should be appropriate and may include backflushing, chemical and/or thermal sanitization and frequent regeneration.
- 4.2.11 The quality of drinking-water should be monitored routinely to account for environmental, seasonal or supply changes which may have an impact on the source water quality.
- 4.2.12 Where drinking-water is stored and distributed by the user, the storage and distribution systems should minimize the degradation of the water quality prior to use. After any such storage, testing should be carried out routinely and in accordance with a defined procedure. The storage and distribution of drinking-water should be done in a manner to ensure a turnover or recirculation of the water, if possible.
- 4.2.13 The equipment and systems used to produce and store drinking-water should be able to be drained or flushed, and sanitized.
- 4.2.14 Storage tanks should be closed with appropriately protected vents and should allow for visual inspection.
- 4.2.15 Distribution pipework should be able to be drained or flushed, and sanitized.

- 4.2.16 The scope and extent of commissioning for the system should be identified and justified.
- 4.2.17 If possible, the results from testing drinking-water should be subjected to statistical analysis in order to identify trends and changes. If the drinking-water quality changes significantly, but is still within specification, the direct use of this water as a WPU, or as the feedwater to downstream treatment stages, should be reviewed for any potential risks. The appropriate action should be taken and documented.
- 4.2.18 Changes to an in-house system or to its operation should be made in accordance with change control procedures.
- 4.2.19 Additional testing should be considered if there is any change in the raw water source, treatment techniques or system configuration.

4.3 Bulk purified water

- 4.3.1 Bulk purified water (BPW) should meet the relevant pharmacopoeial specifications for chemical and microbiological purity. The appropriate and applicable test procedures should be followed.
- 4.3.2 BPW should be prepared from drinking-water as a minimum-quality feedwater.
- 4.3.3 Any appropriate, qualified purification technique, or sequence of techniques, may be used to prepare BPW. BPW could be prepared by, for example, ion exchange, reverse osmosis (RO), RO/electro-deionization (EDI), ultrafiltration, or any combination of these techniques.
- 4.3.4 The following are examples of aspects that should be considered when configuring a water purification system or defining URS:
 - the quality of feedwater and its variation over seasons;
 - the quantity of water required by the user;
 - the required water-quality specification;
 - the sequence of purification stages required;
 - the number and location of sampling points
 - design of sampling points in such a way so as to avoid potential contamination;
 - unit process steps provided and documented with the appropriate instrumentation to measure parameters such as flow, pressure, temperature, conductivity and total organic carbon;

- material of construction;
 - sanitization strategy;
 - main components;
 - interlocks, controls and alarms; and
 - appropriate software, electronic data management, system security and audit trail.
- 4.3.5 Ambient-temperature systems such as ion exchange and ultrafiltration are especially susceptible to microbiological contamination, particularly when equipment is static during periods of no or low demand for water. Sanitization at defined intervals (e.g. based on the data collected from the system validation and system behaviour), as well as other controls, should be defined to prevent and minimize microbiological contamination.
- 4.3.6 Methods for sanitizing each stage of purification should be appropriate and validated. The removal of any agents used for sanitization should be proven.
- 4.3.7 The following controls, for example, should be considered in order to minimize microbial contamination:
- the maintenance of water flow at all times in the storage and distribution system to prevent water from stagnating;
 - control of temperature in the system, for example, by heat exchangers or room cooling in order to reduce the risk of microbial growth;
 - the provision of ultraviolet disinfection at appropriate locations in the system;
 - the use of water-treatment system components that can periodically be thermally sanitized above 70 °C for a defined period of time, or chemically sanitized using, for example, ozone, hydrogen peroxide and/or peracetic acid; and
 - a combination of thermal and chemical sanitization, if required.
- 4.3.8 BPW should have appropriate alert and action limits for chemical and microbiological purity determined from a knowledge of the system and data trending. BPW should be protected from recontamination and microbial proliferation.

4.4 Bulk water for injections

- 4.4.1 BWFI should meet the relevant pharmacopoeial specifications for chemical and microbiological purity (including endotoxins). BWFI is the highest quality of pharmacopoeial WPU.

- 4.4.2 BWFI is not a final dosage form. It is an intermediate bulk product suitable to be used as an ingredient during formulation.
- 4.4.3 As a robust technique should be used for the production of BWFI, the following are examples of what should be considered when configuring a water purification system or defining URS:
- the quality of feedwater and its variation over seasons;
 - the quantity of water required by the user;
 - the required water-quality specification;
 - the sequence of purification stages required, where appropriate;
 - based on the selection of components, material of construction and type of system, the appropriate URS, qualification and validation;
 - the optimum generator size or generators with variable control to avoid over-frequent start/stop cycling;
 - blow-down and dump functions;
 - cool-down venting to avoid contamination ingress;
 - appropriately located sampling points designed in such a way so as to avoid potential contamination;
 - appropriate instrumentation to measure parameters as required;
 - sanitization strategy;
 - interlocks, controls and alarms; and
 - electronic data storage, system security and audit trail.
- 4.4.4 BWFI may be prepared, for example, by distillation as the final purification step. Alternatively, BWFI may be produced by means other than distillation. Techniques such as deionisation, electro deionization, nanofiltration, ultrafiltration, water-softening, descaling, pre-filtration and degasification, ultraviolet treatment, along with other techniques, may be considered in conjunction with a single or double pass RO system. For full details, see *Production of water for injection by means other than distillation* as published in the WHO Technical Report Series, No. 1025, Annex 3, 2020 (6).
- 4.4.5 BWFI should have appropriate microbial and chemical alert and action limits and should also be protected from recontamination and microbial proliferation.

5. General considerations for water purification systems

- 5.1 Pharmaceutical manufacturers should apply the current principles of quality risk management (7) in selecting and using the appropriate water purification systems. An appropriate method for the production of WPU should be used.
- 5.2 Risks and controls should be identified for each stage of the production, storage, distribution, use and monitoring of WPU.
- 5.3 Risks identified should be evaluated in order to determine the scope and extent of validation and qualification of the system, including the computerized systems used for the production, control and monitoring of WPU.
- 5.4 Risk management should be an ongoing part of the quality management process for WPU. A mechanism to review or monitor events associated with the production, storage, distribution and use of WPU should be implemented.
- 5.5 Procedures for managing changes and deviations should be followed. Where applicable, the appropriate risk and impact assessments should be carried out in such a way that changes and deviations are managed.
- 5.6 The chosen water purification system, method or sequence of purification steps must be appropriate in order to ensure the production of water of the intended grade. Based on the outcome of the risk assessment, the following should at least be considered when selecting the water treatment system and method:
 - the quality of the available feedwater and the variation over time (seasonal changes);
 - the availability of suitable support facilities for the system (e.g. electricity, heating, steam, chilled water and compressed air);
 - the extent of pre-treatment required;
 - the sequence of purification steps required;
 - the design and location of sampling points;
 - the sanitization strategy;
 - the availability of water-treatment equipment on the market;
 - the reliability and robustness of the water-treatment equipment in operation;
 - the yield or efficiency of the purification system;
 - the ability to adequately support and maintain the water purification equipment;

- the continuity of operational usage considering hours/days/years and planned downtime;
- the total life-cycle of the system (including capital, operation and maintenance);
- the final water quality specification; and
- the minimum, average and maximum quantity of water required by the user.

5.7 The specifications for water purification equipment, storage and distribution systems should take into account at least the following:

- the location of the plant room;
- the extremes in temperature that the system will encounter;
- the risk of contamination, for example, from materials of construction (contact materials) and the environment;
- the adverse impact of adsorptive contact materials;
- hygienic or sanitary design, where required;
- corrosion resistance;
- freedom from leakage;
- system configuration to avoid or minimize proliferation of microbiological organisms;
- tolerance to cleaning and sanitizing agents (thermal and/or chemical);
- the sanitization strategy;
- system capacity and output requirements; and
- the provision of all necessary instruments, test and sampling points in order to allow for all the relevant critical quality parameters of the complete system to be monitored.

5.8 The design, configuration and layout of the water purification equipment, storage and distribution systems should also take into account the following physical considerations:

- the ability to collect samples;
- the space available for the installation and environment around the system;
- structural loadings on buildings;
- the provision of adequate access for maintenance and monitoring; and
- the ability to safely handle regeneration and sanitization chemicals.

6. Water storage and distribution systems

- 6.1 Where drinking water is stored and distributed, the appropriate controls should be determined and implemented in order to mitigate risks. This applies to all stages in the supply, storage and distribution of drinking-water.
- 6.2 The water storage and distribution systems for PW and BWFI should be appropriately designed, installed, qualified, operated and maintained in order to ensure the storage and distribution of water is of consistent quality to the user points.

7. Good practices for water systems

- 7.1 The components of water systems, including but not limited to pipework, valves and fittings, seals, diaphragms and instruments, should be appropriate and remain suitable during the full range of operational conditions such as temperature and pressure of the system at rest, in operation and during sanitization. The construction materials should be of adequate quality.
- 7.2.1 As a minimum, the following design and construction practices should be considered.

For drinking water storage, supply and distribution systems on-site

Materials of construction should be selected based on the following requirements:

- ability to operate at the temperatures/pressures required;
- lack of impact on the final water quality;
- resistant to sanitizing chemicals;
- threaded and flanged joints are permitted; and
- sample valves should preferably be of sanitary design.

Note that the system may have a design life at the end of which it should be replaced or adequately modified.

For purified water and bulk water for injection systems

Note: Construction standards are generally aligned with potable water standards up to the process stage (e.g. RO).

- Materials of construction should be appropriate. It should be non-leaching, non-adsorbing, non-absorbing and resistant to corrosion. Stainless-steel grade 316L or polyvinylidene chloride (PVDC) is generally recommended. The choice of material should take into account the intended sanitization method.

- Stainless steel systems should be orbitally welded, with manual welds where necessary. Inter-weldability between materials should be demonstrated with the maintenance of weld quality through a defined process. Documentation for such a system should be kept and should include, as a minimum, the qualification of the welder, set-up for welding (e.g. machine), work session test pieces (coupons or weld samples), proof of quality of gas used, welding machine calibration record, weld identification and heat numbers, and logs of all welds. Records, photographs or videos of inspection of a defined proportion of welds (e.g. 100% of manual welds, 10% of orbital welds).
- Joints should be made using sanitary connections, for example, hygienic clamp joints. Threaded joints should not be permitted. Polyvinylidene fluoride or polyvinylidene difluoride (PVDF) systems should be fusion joined and visually inspected.
- Passivation should be considered for stainless steel systems, for example, for non-electropolished surfaces (after initial installation and after significant modification) in accordance with a documented procedure defining the solution to be used, its concentration, the temperature and contact time.
- Internal finish should be smooth.
- Flanges, unions and valves should be of a hygienic or sanitary design. Valves should be diaphragm type forged or machined body, with points of use constructed so that they can drain. Sample valves should be sanitary type with the surface roughness of 1.0 micrometer RA or lower for PW and WFI systems and are typically installed between process stages and on the distribution loop return. The appropriate checks should be carried out in order to ensure that the correct seals and diaphragms are used and that they are fitted and tightened correctly.
- The system should be installed to promote drainability with a recommended minimum slope of 1/100.
- Where appropriate, pressure or hydro-tests for leaks, spray-ball functionality test and flow turbulence should be considered.
- Provision should be made for in-line measurement for total organic carbon (TOC), conductivity, pressure, flow and temperature.
- Documents should provide evidence of system components and qualification. These include as applicable drawings, original or certified copies of certificates of conformity for materials of construction, records of on-site tests performed, weld/joining records, calibration certificates, system pressure test records and records of passivation.

8. System sanitization and bioburden control

- 8.1 Water-treatment, storage and distribution systems should be subjected to controls that will reduce the risk of contamination and the proliferation of microbiological organisms.
- 8.2 Controls may include using chemical and/or thermal sanitization procedures as appropriate for production, storage and distribution systems. The procedure and conditions used (such as times and temperatures, as well as the frequency), should be defined and proven to be effective for sanitizing all relevant parts of the system. The techniques employed should be considered during the design stage of the system as the procedure and technique may impact on the components and materials of construction.
- 8.3 Systems that operate and are maintained at elevated temperatures (e.g. > 70 °C) are generally less susceptible to microbiological contamination than systems that are maintained at lower temperatures. When lower temperatures are required due to the water treatment processes employed, or the temperature requirements for the water in use, special precautions should be taken to prevent the ingress of contaminants including microorganisms (see section 9.2 for guidance).
- 8.4 Where the chemical sanitization of the water systems is part of the biocontamination control programme, a validated procedure should be followed in order to ensure that the sanitizing process selected is effective and that the sanitizing agent has been effectively removed.
- 8.5 Records of sanitization should be maintained.
- 8.6 Other control techniques to be considered may include:
 - The maintenance of a continuous circulation of water maintaining turbulent flow evidenced by, for example, a Reynolds number of > 4000.
 - Ensuring hygienic design, including the use of zero dead leg diaphragm valves where possible, and minimizing dead legs elsewhere. Areas of possible dead legs should be measured and calculated.
 - Installing pipework in a manner to allow for full drainage, if required. A guidance figure for the slope is not less than 1/100.
 - Considering the use of ultraviolet lamps in the system where needed with independent monitoring.
 - Maintaining the system at an elevated temperature (e.g. > 70 °C), if required.

9. Storage vessels

- 9.1 Storage vessels should be appropriate for their intended use.
- 9.2 As a minimum, the following should be considered:
- the design and shape to ensure drainage of water from the vessel, when required;
 - construction materials;
 - capacity, including buffer capacity, between the steady state, water generation rate and the potentially variable simultaneous demand from user points, short-term reserve capacity in the event of failure of the water-treatment system or the inability to produce water (e.g. due to a regeneration cycle);
 - prevention of stagnant water in the vessel (e.g. the headspace where water droplets can accumulate) and the need for the use of a spray-ball or distributor devices to wet the inner surfaces of the vessel;
 - the fitting of bacteria-retentive, hydrophobic vent filters which are tested for their integrity at appropriate intervals;
 - the fitting of sanitary design pressure safety valves or bursting discs provided with external rupture indicators to ensure that loss of system integrity is detected;
 - the design and sanitization, as required, of level indicators;
 - the design and location of valves, sampling points and monitoring devices and sensors; and
 - the need for heat exchangers or jacketed vessels. Where these are used, double tube sheet or double plate heat exchangers should be considered.

10. Water distribution

- 10.1 The water distribution system should be designed as a loop, with continuous circulation of BPW and BWFI. Where this is not the case, the appropriate justification for using a non-recirculating one-way system should be provided as well as robust measures implemented to monitor these.

- 10.2 As a minimum, the following should be considered:

- controls to minimize proliferation of contaminants;
- material of construction, joints and impact as a result of sanitization; and
- the design and location of devices, sensors and instruments such as flow meters, conductivity sensors, TOC analysers and temperature sensors.

- 10.3 Filtration should not be used in distribution loops or at take-off user points.
- 10.4 Where heat exchangers are used, they should be arranged in continually circulating loops or sub-loops in order to avoid unacceptable static water in the system.
- 10.5 When the temperature is reduced for processing purposes, the reduction should occur for the minimum necessary time. The cooling cycles and their duration should be proven satisfactory during the qualification of the system.
- 10.6 Circulation pumps should be of a sanitary design with the appropriate seals to prevent contamination of the system.
- 10.7 Where stand-by pumps are provided, they should be configured or managed to avoid zones where stagnant water is trapped within the system.
- 10.8 Consideration should be given to preventing contamination in systems where parallel pumps are used. There should be no stagnant water remaining in a pump when the pumps is not being used.
- 10.9 Components should be identified and labelled. The direction of flow should be indicated.

11. Operational considerations including some qualification and validation principles

- 11.1 Water systems should be appropriately qualified and validated (8). The scope and extent of qualification should be determined based on risk assessment. (See also point 3.3. above.)
- 11.2 When commissioning work is done, this should be documented. Commissioning is not a replacement for qualification.
- 11.3 In order to demonstrate the reliability and robustness of a system and its performance, a three-phase approach should be used for validation, covering at least one year of operation over different seasons. Tests on the source water (drinking-water) should be included within the validation programme and continued as part of the routine monitoring, and these results should meet specifications.

Note: A typical phase 1 to 3 approach for a new system is described below. When changes are made to existing systems, the phase(s) and length of each phase, as well as sampling points and frequency of sampling should be based on documented risk assessment.

Phase 1

Phase I should cover a period of at least two weeks.

Procedures and schedules should cover at least the following activities and testing approaches:

- chemical and microbiological testing in accordance with a defined plan;
- sample, test and monitoring of the incoming feedwater to verify its quality;
- sample, test and monitoring after each step in the purification process;
- sample, test and monitoring at each point of use and at other defined sample points including the end of the distribution loop;
- verification of operating ranges;
- operating, cleaning, and maintenance;
- sanitizing procedures and operating ranges;
- demonstrate the consistent production and delivery of product water of the required quality and quantity;
- establishing provisional alert and action levels; and
- test-failure procedure.

The system should be monitored intensively for its performance. Water should not be used for product manufacturing during this phase.

Phase 2

Phase 2 should cover at least a further test period of two weeks after the satisfactory completion of Phase 1. The system should be monitored while deploying all the standard operating procedures (SOPs). The sampling programme should be generally the same as in Phase 1. The use of the water for product manufacturing purposes during this phase may be acceptable, provided that Phase 1 and ongoing Phase 2 data demonstrate the appropriate water quality and the practice is approved by QA.

The approach should also:

- demonstrate consistent system operation within established ranges; and
- demonstrate consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOPs.

Phase 3

Phase 3 should follow phase 2 ensuring that the duration of Phase I, 2 and 3 cover at least 12 months. The sample locations, sampling frequencies and tests may be

reduced according to a routine plan which should be based on the established procedures and data from Phase 1 and Phase 2. Data should be trended, for example, quarterly and a system review should be undertaken after the completion of Phase 3 as part of the evaluation of system performance capability. The appropriate action should be taken where such a need is identified.

Water can be used during this phase. The data and information obtained during Phase 3 should demonstrate the reliable performance of the system over this period of time covering the different seasons.

12. Continuous system monitoring

- 12.1 The system should be subject to continuous monitoring.
- 12.2 A monitoring plan should be followed where samples are collected in accordance with a written procedure.
- 12.3 A combination of online and offline instruments, linked to appropriately qualified alarm systems, should be used. Parameters such as flow, pressure, and temperature should be monitored with online instruments – as well as conductivity and TOC, where possible. Periodic offline testing to confirm the results from online testing is recommended. Other parameters may be monitored through offline testing.
- 12.4 Offline testing (including physical, chemical and microbiological attributes) should be done in accordance with a predetermined programme.
- 12.5 Samples should be taken from points of use and dedicated sample points where required. All water samples should be taken using the same methodology as detailed in production procedures, for example, using a hose and with a suitable flushing and drainage procedure in place.
- 12.6 Tests should be carried out to ensure that the relevant pharmacopoeia specification (and approved company specification, where applicable) has been met. This may include the microbiological quality of water, as appropriate.
- 12.7 The results for identified quality attributes should be subjected to statistical analysis at defined intervals, for example, monthly, quarterly and annually, in order to identify trends. The results should be within defined control limits, such as 3 sigma.
- 12.8 Alert and action levels should be established based on historically reported data.
- 12.9 Adverse trends and out-of-limit results should be investigated for the root cause, followed by the appropriate corrective and preventive actions. Where microbial contamination of BWFI occurs, the micro-organism should be identified.

13. Maintenance of water systems

13.1 WPU systems should be maintained in accordance with an approved and documented maintenance programme. Records should be kept.

13.2 The maintenance programme should take into account at least the following:

- defined frequency for system elements e.g. filters, instruments, gauges;
- the calibration programme;
- SOPs for specific tasks;
- the control and storage of approved spare parts;
- preventive maintenance and maintenance plan and instructions, including cleaning after maintenance;
- a review and approval of systems for use upon completion of work; and
- a record and review of problems and faults during maintenance

14. System reviews

14.1 WPU systems should be reviewed at described intervals (e.g. annually). The review should be documented.

14.2 The review team should be comprised of representatives from, for example, engineering, utilities, validation, QA, quality control, microbiology, production and maintenance.

14.3 Examples of matters to be included in the review are:

- changes made since the last review;
- system performance trends and capability;
- quality trends;
- failure events and alarm history;
- investigations;
- out-of-specification and out-of-limit results;
- alert and action limits;
- assessing compliance with current GMP requirements for WPU systems;
- verification of documentation being current;
- maintenance and calibration history;
- records such as log books and electronic data; and
- the appropriateness of the software and the computerized system linked to the water system, for example, SCADA (Supervisory Control and Data

Acquisition), including audit trail, authorized users with access and privileges.

15. Inspection of water systems

- 15.1 WPU (BPW and BWFI) systems are subjected to regulatory inspections. Users should conduct audits and self-inspection of water systems at regular intervals. Records should be maintained.
- 15.2 This document can be used as the basis of an audit and inspection. A tour of the water system, treatment system, storage and distribution system, as well as visible pipework and user points, should be performed to ensure that the system is appropriately designed, installed, qualified, validated, maintained and monitored.

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1.5 Production of water for injection by means other than distillation

**Annex 3, WHO Technical Report Series, 1025,
2020 (new)**

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1. Introduction

- 1.1 Water is widely used in the pharmaceutical industry. It is often used as a raw material; an ingredient in formulations; to prepare reagents; in cleaning; and in the manufacture of active pharmaceutical ingredients), intermediates and finished pharmaceutical products.
- 1.2 Water for pharmaceutical use must meet quality requirements and specifications, as published in relevant standards and pharmacopoeias. Water of the required quality for its intended use should be produced by appropriate methods.

2. Scope

- 2.1 This document provides guidance for the production of water for injection (WFI) by means other than distillation. The principles described in this guideline may be applied to other grades of water, meeting other specifications.
- 2.2 The document is not exhaustive but aims to provide guidance on the main principles to be considered. Other guidelines and literature should also be consulted (1, 2).

3. Monographs

- 3.1 Manufacturers should have appropriate specifications for WFI.
- 3.2 Monographs for WFI are published in The International Pharmacopoeia (1), as well as various national pharmacopoeias, and provide for the minimum requirements for the quality of WFI.
- 3.3 WFI should meet the specification as published in current monographs of the relevant pharmacopoeia recognized by the national medicines regulatory authority.

4. Life-cycle approach

- 4.1 Good practices during each stage of the life-cycle of WFI should be considered.
- 4.2 Stages include, but are not limited to, the collection and treatment of source water; treatment of drinking water; treatment of purified water; and the production, storage, distribution, use and control of WFI.
- 4.3 Principles of risk management (3) and data governance should be applied in each relevant stage of the life-cycle.

5. Risk assessment

- 5.1 An appropriate method for the production of WFI should be used.
- 5.2 Risks and controls should be identified for each stage of the life-cycle of the production, storage, distribution, use and control of WFI.
- 5.3 Risks identified should be analysed and evaluated to determine the scope and extent of validation and qualification of the system, including the computerized controls used for the production, control and monitoring of WFI. Risk management should be an ongoing part of the quality management process for WFI. A mechanism to review or monitor events associated with production, storage, distribution and use of WFI should be implemented.
- 5.4 Where production methods other than distillation are used, specific attention should be given to ensure:
 - the appropriateness of user requirement specifications;
 - feed-water quality;
 - the sequence of purification stages required;
 - the extent of pretreatment required;
 - appropriately designed and located sampling points;
 - controls are in place to prevent “dead legs”; and
 - in-line monitoring.

6. Control strategy

- 6.1 The WFI system should be appropriately qualified and validated.
- 6.2 There should be controls to minimize the risk of contamination of WFI produced, stored or circulated.
- 6.3 An appropriate control strategy should be defined to ensure that all risks identified are eliminated, or reduced to an acceptable level.
- 6.4 All parts of the system (pretreatment, treatment, storage and distribution) should be appropriately designed and constructed. Materials for construction should not be reactive, additive, absorptive or adversely affect the quality of water and should be suitable for the sanitizing method used.
- 6.5 Treatment (also referred to as pretreatment) of water entering the system should ensure adequate removal of chemicals (organic and inorganic), particles, matter

and microbiological impurities. The treatment should not have a detrimental effect on the materials of construction or downstream components of the water system.

- 6.6 Techniques such as deionization, electro-deionization, nanofiltration, ultrafiltration, water softening, scaling, prefiltration, degasification, and ultraviolet treatment, along with other techniques, may be considered in conjunction with a single- or double-pass reverse osmosis system.
- 6.7 These should allow for sanitization (thermal or chemical, or a combination thereof) when required. The method of sanitization should be appropriate, effective and validated. Sanitization should be done at specified intervals, in accordance with a documented procedure.
- 6.8 Appropriate sampling techniques should be used to sample water for analysis, at defined sampling locations, in accordance with a documented sampling procedure and a schedule.

7. Good practices in the production of water for injection

- 7.1 WFI should be prepared either from water that complies with World Health Organization guidelines for drinking water (4), national standards for drinking water as a minimum quality feedwater, or purified water.
- 7.2 The results of water testing should be trended. Trend data should be reviewed routinely, in order to determine the potential for deterioration in the system.
- 7.3 Appropriate alert and action limits, in addition to specification limits, should be specified. Trend data should be assessed routinely and used to revise limits where appropriate.
- 7.4 The system should be monitored for its ongoing performance within defined parameters, including but not limited to, conductivity, total organic carbon (TOC) and microbial contamination.
- 7.5 A combination of online and offline monitoring of WFI should be done, to ensure that the appropriate water specification is maintained. TOC and conductivity should be monitored with online instruments. Use of rapid microbiological methods is encouraged for timely monitoring, and aids with rapid responses to prevent deterioration of the system.
- 7.6 The outlet of reverse osmosis systems should be monitored, to ensure that potential breaches are identified. This may include monitoring the conductivity of the water, and pressure.

7.7 The system should remain in a validated state throughout its life-cycle.

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1.6 Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products

Annex 8, WHO Technical Report Series, 1010,
2018

Background

The World Health Organization (WHO) published the first edition of the *WHO Guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* in 2006 (1). After a revision, the second edition of the document was published in 2011 (2). Consideration of various comments and questions related to good manufacturing practices (GMP) for heating, ventilation and air-conditioning (HVAC) systems led to the proposal to revise the document. After wide public consultation, and taking into account comments received, the document and comments were discussed during an informal consultation in Geneva in April 2017.

During this informal consultation the proposed changes based on comments received as well as additional suggestions made during the consultation, were discussed. It was agreed that the guidelines be amended to comprise two documents: one that would consist of guidelines containing recommendations for GMP for HVAC systems for non-sterile products and a second document that would contain examples and drawings that would clarify some of the recommendations made in the first document.

Therefore, the previous version of the *WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* as published in 2011 (2) should be amended according to these new guidelines.

Summary of main changes

In accordance with the recommendation made during the informal consultation in April 2017, the guidelines have been rewritten in two parts. The present document is the first part and contains the recommendations that are to be considered as good practices in design, management, control and qualification over the life cycle of HVAC systems.

The second part will contain non-binding examples, clarifications and drawings in support of the guidelines in the present document and is currently being drafted.

No summary of changes is provided here, as the content of the previous guidelines has been reorganized taking into account all the comments received during the last comment period.

The illustrative guidance and explanations (second part) will be published separately.

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1. Introduction

Heating, ventilation and air-conditioning (HVAC) play an important role in ensuring the manufacture of quality pharmaceutical products. The good manufacturing practice (GMP) requirements for the prevention of contamination and cross-contamination are an essential design consideration of an HVAC system. A well-designed HVAC system also provides for protection of the environment and the operators as well as comfortable working conditions.

These guidelines mainly focus on recommendations for HVAC systems used in facilities for the manufacture of non-sterile dosage forms, which include tablets, capsules, powders, liquids, creams and ointments. The general HVAC system design principles contained in these guidelines may, however, also be applied to other dosage forms.

HVAC system design influences architectural building design and layout, for example, with regard to airlock positions, doorways and lobbies. These in turn have an effect on room pressure, pressure differentials, pressure cascades, contamination and cross-contamination control. Therefore, the design of the HVAC system should be considered at the initial design stage of a pharmaceutical manufacturing plant.

Temperature, relative humidity and ventilation should be appropriate and should not adversely affect the quality of pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment and instruments.

A comprehensive science- and risk-based approach should be followed throughout the life-cycle of an HVAC system, including its design, qualification and maintenance. Risk assessment is, however, not a substitute for GMP (3).

2. Scope

These guidelines focus primarily on GMP for the design, qualification, management and maintenance of HVAC systems in facilities for the manufacture of non-sterile dosage forms. They are intended to complement the guidelines on GMP for pharmaceutical products and should be read in conjunction with the parent guide. The additional standards addressed in these guidelines should therefore be considered supplementary to the general requirements set out in the main principles guide (4).

Most of the system principles described in these guidelines may also be considered in facilities manufacturing other dosage forms and products, and finishing processing steps for active pharmaceutical ingredients (APIs). Additional, specific requirements may apply for air-handling systems for pharmaceutical products containing hazardous substances, sterile products and biological products. These are covered in separate WHO guidelines (3, 5) and working document WHO/BS/2015.2253, intended to replace (6), respectively.

3. Glossary

The definitions given below apply to terms used in this document. They may have different meanings in other contexts.

acceptance criteria. Numerical limits, ranges or other suitable measures for acceptance of test results.

action limit. The action limit is reached when the acceptance criteria of a critical parameter have been exceeded. Results outside these limits will require specified action and investigation.

air changes per hour. The flow rate of air supplied to a room, in m³/hour, divided by the room volume, in m³.

air-handling unit (AHU). The AHU serves to condition the air and provide the required airflow within a facility.

airflow protection booth. A booth or chamber, typically for purposes of carrying out sampling or weighing, in order to provide product containment and operator protection.

airlock. An enclosed space with two or more doors, which is interposed between two or more rooms, for example, of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods (personnel airlock (PAL); material airlock (MAL)).

alert limit. The alert limit is reached when the normal operating range of a critical parameter has been exceeded, indicating that corrective measures may need to be taken to prevent the action limit being reached.

as-built. Condition where the installation is complete, with all services connected and functioning but with no production equipment, materials or personnel present.

at-rest. Condition where the installation is complete, with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.

central air-conditioning unit (see air-handling unit).

change control. A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

clean area (cleanroom). An area (or room or zone) with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

clean-up (see recovery).

closed system. A system where the product or material is not exposed to the manufacturing environment.

commissioning. Commissioning is the documented process of verifying that the equipment and systems are installed according to specifications, placing the equipment into active service and verifying its proper action. Commissioning takes place at various stages during project construction but prior to validation.

containment. A process or device to contain product, dust or contaminants in one zone, preventing it from escaping to another zone.

contamination. The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediate, during production, sampling, packaging or repackaging, storage or transport.

controlled area (classified area). An area within the facility in which specific procedures and environmental parameters, including viable and non-viable particles, are defined, controlled and monitored to prevent degradation, contamination or cross-contamination of the product.

controlled not classified. An area where some environmental conditions or other attributes (such as temperature) are controlled, but the area has no cleanroom classification.

critical parameter or component. A processing parameter (such as temperature or relative humidity) that affects the quality of a product, or a component that may have a direct impact on the quality of the product.

critical quality attribute. A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality.

cross-contamination. Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

cross-over bench. Cross-over or step-over bench in the changing room to demarcate the barrier between different garment change procedures.

design condition. Design condition relates to the specified range or accuracy of a controlled variable used by the designer as a basis for determining the performance requirements of an engineered system.

design qualification. The documented check of planning documents and technical specifications for design conformity with the process, manufacturing, good manufacturing practices and regulatory requirements.

differential pressure. The difference in pressure between two points, such as the pressure difference between an enclosed space and an independent reference point, or the pressure difference between two enclosed spaces.

direct impact system. A system that is expected to have a direct impact on product quality. These systems are designed and commissioned in line with good engineering practice and, in addition, are subject to qualification practices.

exfiltration. The egress of air from a controlled area to an external zone.

extract air. Air leaving a space, which could be either return air or exhaust air. Return air refers to air that is returned to the air-handling unit and exhaust air is air that is vented to the atmosphere.

facility. The built environment within which the clean area installation and associated controlled environments operate together with their supporting infrastructure.

good engineering practice. Established engineering methods and standards that are applied throughout the project life cycle to deliver appropriate, cost-effective solutions.

hazardous substance or product. A product or substance that may present a substantial risk of injury to health or to the environment.

HEPA filter. High-efficiency particulate air filter.

HVAC. Heating, ventilation and air-conditioning. Also referred to as “environmental control systems”.

indirect impact system. A system that is not expected to have a direct impact on product quality, but typically will support a direct impact system. These systems are designed and commissioned according to good engineering practice only.

infiltration. Infiltration is the ingress of air from an external zone into a controlled area.

installation qualification. Documented verification that the premises, HVAC system, supporting utilities and equipment have been built and installed in compliance with their approved design specification.

ISO 14644. The International Standards Organization (ISO) has developed a set of standards for the classification and testing of cleanrooms. Where ISO 14644 is referenced it implies the latest revision and all its separate parts.

no-impact system. A system that will not have any impact, either directly or indirectly, on product quality. These systems are designed and commissioned according to good engineering practice only.

noncritical parameter or component. A processing parameter or component within a system whose operation, contact, data control, alarm or failure will have an indirect impact or no impact on the quality of the product.

normal operating range. The range that the manufacturer selects as the acceptable values for a parameter during normal operations. This range must be within the operating range.

operating limits. The minimum and/or maximum values that will ensure that product and safety requirements are met.

operating range. The range of validated critical parameters within which acceptable products can be manufactured.

operational condition. This condition relates to carrying out room classification tests with the normal production process with equipment in operation and the normal staff present in the specific room.

operational qualification. This is the documentary evidence to verify that the equipment operates in accordance with its design specifications within its normal operating range and performs as intended throughout all anticipated operating ranges.

oral solid dosage form. Usually refers to solid dosage forms of medicinal products such as tablets, capsules and powders to be taken orally.

pass-through hatch or pass box. A cabinet with two or more doors for passing equipment, material or product while maintaining the pressure cascade and segregation between two controlled zones. A passive pass-through hatch (PTH) has no air supply or air extraction. A dynamic PTH has an air supply into the chamber.

performance qualification. The documented verification that the process and/or the total process related to the system performs as intended throughout all anticipated operating ranges.

point extraction. Air extraction point located so that it effectively captures dust near its source.

pressure cascade. A process whereby air flows from one area, which is maintained at a higher pressure, to another area maintained at a lower pressure.

qualification. The planning, carrying out and recording of tests on equipment and a system, which forms part of the validated process, to demonstrate that it will perform as intended.

quality critical process parameter. A process parameter that could have an impact on the critical quality attribute.

recovery. Room recovery or clean-up tests are performed to determine whether the installation is capable of returning to a specified cleanliness level within a finite time, after being exposed briefly to a source of airborne particulate challenge.

relative humidity. The ratio of the actual water vapour pressure of the air to the saturated water vapour pressure of the air at the same temperature expressed as a percentage. More simply put, it is the ratio of the mass of moisture in the air, relative to the mass at 100% moisture saturation, at a given temperature.

standard operating procedure. An authorized written procedure, giving instructions for performing operations, not necessarily specific to a given product or material, but of a more general nature (for example operation of equipment, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain standard operating procedures may be used to supplement product-specific master and batch production documentation.

turbulent air flow. Turbulent flow, or non-unidirectional airflow, is air distribution that is introduced into the controlled space and then mixes with room air by means of induction.

unidirectional airflow. A rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (see also turbulent air flow). (Modern standards no longer refer to laminar flow, but have adopted the term unidirectional airflow.)

validation. The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

validation master plan. A high-level document that establishes an umbrella validation plan for the entire project and is used as guidance by the project team for resource and technical planning (also referred to as a master qualification plan).

4. Premises

- 4.1 The manufacture of non-sterile pharmaceutical products should take place in a controlled environment, as defined by the manufacturer.
- 4.2 The design of the HVAC system should be closely coordinated with the architectural design of the building.
- 4.3 Infiltration of unfiltered air into a manufacturing facility should be prevented as this can be a source of contamination.
- 4.4 Manufacturing facilities should normally be maintained at a positive pressure relative to the outside, to prevent the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to the outside, special precautions should be taken to mitigate any risks (see (3)).
- 4.5 Areas for the manufacture of products, especially where materials and products are exposed to the environment, should be of an appropriate level of cleanliness. The level of air cleanliness for different areas should be determined according to, but not limited to, the products manufactured, the process used and the products' susceptibility to degradation.
Where a clean room classification is specified, the manufacturer should state whether the classification is rated for the "as-built", "at-rest" or "operational" condition.
- 4.6 HVAC systems should ensure that the specified room conditions are attained, for example through heating, cooling, air filtration, air distribution, airflow rates and air exchange rates.
- 4.7 Any area where pharmaceutical starting materials, products, primary packing materials, utensils and equipment are exposed to the environment should have the same level of cleanliness or classification as the area in which the products are produced.
- 4.8 Appropriate design and controls for the premises and HVAC systems should be in place to achieve containment, cleanliness and the appropriate levels of protection of the product, personnel and the environment.

Note: For facilities where the highest level of containment is a requirement, refer to the guidance in *WHO good manufacturing practices for pharmaceutical products containing hazardous substances* (3).

4.9 Containment, cleanliness and protection may be facilitated through, for example:

- correct building layout;
- building finishes;
- the use of airlocks such as personnel airlocks (PAL) and/or material airlocks (MAL);
- pass-through hatches (PTH);
- change rooms and passages;
- sufficient pressure differentials.

4.10 Detailed schematic diagrams should be maintained, indicating, for example, air supply and air return, room pressure differentials and airflow directions.

4.11 Where possible, personnel and materials should not move from a higher cleanliness zone to a lower cleanliness zone and back to a higher cleanliness zone. Where this is unavoidable, risks should be identified and controlled.

4.12 The final change room should be at the same cleanliness level (at rest) as the area into which it leads.

4.13 Where appropriate, such as where the simultaneous opening of airlock doors might lead to a cross-contamination risk, airlock doors should not be opened at the same time. In such cases, controls such as interlocking systems, warning systems and procedures should be implemented.

4.14 Swing doors should normally open to the high-pressure side and be provided with self-closers. Exceptions to the door swing direction should be justified and may include for fire escapes or other health and safety measures. In these cases, door closer mechanisms should be carefully controlled and other controls should be in place to prevent any risk.

4.15 Sampling, weighing and dispensing areas should be appropriately designed to provide the required levels of containment, operator protection and product protection.

4.16 Sampling, weighing and dispensing should be performed under the same environmental conditions as specified in the areas for the next stage of processing of the product.

4.17 Factors such as airflow should not disrupt the accuracy of balances.

4.18 The position of the operator, equipment and containers should not obstruct airflow patterns and result in risks.

- 4.19 Once an area is qualified with a specific layout for operators, equipment and processes, this configuration should be ensured during routine activity.
- 4.20 Return and exhaust filters and grilles selected and installed should be appropriate and their design should facilitate cleaning and maintenance.
- 4.21 The impact and risk to the HVAC system should be considered when changes are planned to an existing facility. This includes upgrades and retrofitting of facilities.

5. Design of HVAC systems and components

HVAC systems should be appropriately designed and managed throughout their life cycle. Documentation such as schematic drawings should be maintained to reflect the current situation.

- 5.1 Risk management principles should be applied for HVAC systems. This includes, but is not limited to, appropriate design, operation and monitoring, control of the climatic conditions and the prevention of contamination and cross-contamination.
- 5.2 The HVAC system capacity should be sufficient to ensure that the required performance is maintained during normal use by taking into consideration, for example, room leakage, duct leakage and filter conditions.
- 5.3 Materials for constructing the components of an HVAC system should not become a source of contamination.
- 5.4 Where possible, ducting, piping, fittings, sensors and other components should be clearly marked or labelled for ease of identification, indicating location and direction of flow as appropriate.
- 5.5 Air intake and exhaust air terminals should be positioned in a manner in relation to one another that assists in preventing cross-contamination.
- 5.6 Air-handling units (AHUs) should be provided with adequately designed drains to remove any condensate that may form in them.
- 5.7 Conditions and limits for parameters such as temperature, relative humidity and air cleanliness should be specified and achieved, as needed, for the materials and products handled, as well as for process risk.
- 5.8 Where appropriate, recovery rates should be specified and achieved to demonstrate that the HVAC system is capable of returning an area to a specified level of cleanliness or classification, temperature, relative humidity, room pressure and microbial limits within the specified time.

- 5.9 Failure mode and effect of critical components should be analysed. The analysis should include possible room pressure changes due to fan failure and possible impact of partial system shutdown on ease of opening doors for escape purposes.
- 5.10 The air distribution and airflow patterns should be appropriate and effective.
- 5.11 Air supply and extract grilles should be appropriately located to provide effective room flushing and to prevent zones of stagnant air.
- 5.12 The performance of HVAC systems should be controlled and monitored to ensure continuous compliance with defined parameters, and records should be maintained. Limits defined should be justified.
- 5.13 Where automated monitoring systems are used, these should be capable of indicating any out-of-limit condition by means of an alarm or similar system. Where these systems are identified as GXP systems, they should be appropriately validated.
- 5.14 Appropriate alarm systems should be in place to alert personnel in case of failure of a critical component of the system, for example, a fan.
- 5.15 The effect of fan failure on building and HVAC components should be assessed. Where appropriate, provision should be made for a fan interlock failure matrix.
- 5.16 Periodic switching off of AHUs, for example, overnight or at weekends, or reducing supply air volumes during non-production hours, should be avoided so that material or product quality is not compromised. Where AHUs are switched off, there should be appropriate justification and no risk to materials or products. The procedure and its acceptability should be proven and documented.
- 5.17 Procedures should be in place and records maintained for the startup and shutdown sequence of AHUs.

6. Full fresh air systems and recirculation systems

- 6.1 Full fresh air or recirculation type HVAC systems may be used. Fresh air should be adequately filtered to remove contaminants. Where recirculation systems are used, there should be no risk of contamination or cross-contamination.
- 6.2 HEPA filters may be installed (in the supply air stream or return air stream) to remove contaminants and thus prevent cross-contamination. The HEPA filters in such an application should have an EN 1822 classification of at least H13 or equivalent.

- 6.3 HEPA filters may not be required to control cross-contamination where evidence that cross-contamination would not be possible has been obtained by other robust technical means, or where the air-handling system is serving a single product facility.
- 6.4 The amount of fresh air intake required should be determined. As a minimum, the following criteria should be considered:
 - sufficient volume of fresh air to compensate for leakage from the facility and loss through exhaust air systems;
 - operator occupancy;
 - regional or national legislation.
- 6.5 Air that might be contaminated with organic solvents or highly hazardous materials should normally not be recirculated.
- 6.6 The need for and the degree of filtration of the exhaust air should be considered based on risk, exhaust air contaminants and local environmental regulations.
- 6.7 Where energy-recovery wheels are used in multiproduct facilities, controls should be in place to ensure that these do not become a source of cross-contamination.

7. Air filtration, airflow direction and pressure differentials

- 7.1 Where different products are manufactured at the same time, i.e. in different areas or rooms in a multiproduct manufacturing site, measures should be taken to ensure that dust cannot move from one room to another. Facility design and layout, appropriate levels of filtration, airflow direction and pressure differentials can assist in preventing cross-contamination.
- 7.2 Filters selected should be appropriate for their intended use and classified according to the current international classification system (see Table A8.1).
- 7.3 Airflow directions should be appropriate, taking operator and equipment locations into consideration.
- 7.4 The pressure differential between areas in a facility should be individually assessed according to the products handled and level of protection required. The pressure differential and the direction of airflow should be appropriate to the product and processing method used, and should also provide protection for the operator and the environment.

- 7.5 The pressure differential should be designed so that the direction of airflow is from the clean area, resulting in dust containment, for example, from the corridor to the cubicle.
- 7.6 The limits for the pressure differential between adjacent areas should be such that there is no risk of overlap in the defined dynamic operating ranges.

- 7.7 Normally, for rooms where dust is liberated, the corridor should be maintained at a higher pressure than the rooms and the rooms at a higher pressure than atmospheric pressure. (For negative pressure facilities refer to *WHO good practices for pharmaceutical products containing hazardous substances* (3), for guidelines and design conditions.)

Room pressure differential indication should be provided. This may be by pressure gauges or suitable electronic systems such as EMS or BMS. Where pressure indication gauges are provided, these should have a range and graduation scale that enables them to be read to an appropriate accuracy. The normal operating range, alert and action limits should be defined and displayed at the point of indication or EMS/BMS.

Room pressure should be traced back to representative ambient pressure (by summation of the room pressure differentials), in order to determine the actual absolute pressure in the room.

- 7.8 The pressure control and monitoring devices used should be calibrated. Compliance with specifications should be regularly verified and the results recorded.
- 7.9 Pressure control devices should be linked to an alarm system which is set according to the levels determined by a risk analysis and justified dead times.
- 7.10 Zero setting of gauges should be tamper proof. Zero setting should be checked at regular intervals.
- 7.11 Where airlocks are used, the pressure differentials selected should be appropriate. When selecting room pressure differentials, transient variations, such as machine extract systems and their impact, should be taken into consideration.

Table A8.1
Comparison of filter test standards – approximate equivalencies^a

(superseded)	Eurovent 4/5 rating	ASHRAE 52.2	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	ISO 29463	
					Average arrestance Am (%) (superseded)	Average dust spot efficiency Em (%) (superseded)
					MPPS integral overall efficiency (%)	EN rating
EU 14					99.99995	U17
EU 13					99.9995	U16
EU 12					99.995	U15
EU 11					99.95	H14
EU 10					99.5	H13
EU 9	Merv 16				99.5	E12
EU 9	Merv 15				95	E11
EU 8	Merv 14				>95	E10
EU 7	Merv 13				95	F9
EU 7					90	F8
EU 7					85	F7
EU 7					80	
						EN 779:2012
						EN 1822:2009
						EN 779 & EN 1822

Table A8.1 *continued*

		ISO 29463		EN 779:2012	
		EN 779 & EN 1822		EN rating	
(superseded)	Merv rating	Average arrestance Am (%) (superseded)	Average dust spot efficiency Em (%) (superseded)	MPPS integral overall efficiency (%)	EN rating
	Merv 12	>95	75		
EU 6		>95	70		M
	Merv 11	>95	65		
		>95	60		
	Merv 10	>95	55		
EU 5	Merv 9	>95	50		M
	Merv 8	>95	45		
		>95	40		
	Merv 7	>90	35		
EU 4		>90	30		G4
	Merv 6	90	25		
EU 3	Merv 5	85	20		G3
		80	<20		

Table A8.1 *continued*

		ISO 29463			
		EN 779 & EN 1822		EN 779: 2012	
(superseded)	Merv rating	Average arrestance Am (%) (superseded)	Average dust spot efficiency Em (%) (superseded)	MPPS integral overall efficiency (%)	EN rating
	Merv 4	75			
EU 2	Merv 3	70		G2	
	Merv 2	65			
EU 1	Merv 1	<65		G1	

^a Ensure that the classification is current.
MPPS; most penetrating particle size.

Note: The filter classifications referred to above relate to the EN 1822:2009 and EN 779: 2012 test standards (EN 779 relates to filter classes G1 to F9 and EN 1822 relates to filter classes E10 to U17.

8. Temperature and relative humidity

- 8.1 Where appropriate, temperature and relative humidity should be controlled, monitored and recorded to ensure that the conditions are maintained pertinent to the materials and products as required, and provide a comfortable environment for the operators.
- 8.2 Limits for minimum and maximum room temperatures and relative humidity should be appropriate taking into consideration, for example, materials and products.
- 8.3 Where steam or humidity is present, controls should be in place to ensure that the HVAC system will remain effective. Precautions should be taken to prevent moisture migration that may increase an uncontrolled load on the HVAC system.
Where humidification or dehumidification is required, this should be achieved by appropriate means that will not become a source of contamination.
- 8.4 Dehumidification and cooling systems should be well drained. Condensate should not accumulate in air-handling systems and should not become a source of contamination.

9. Dust, vapour and fume control

The discharge location of dust, vapours and fumes should be carefully considered to prevent contamination and cross-contamination.

- 9.1 Dust, vapours and fumes could be sources of contamination and should be appropriately controlled. Wherever possible, they should be removed at source. The HVAC system should not normally serve as the primary mechanism of dust control.
- 9.2 Dust extraction systems should be appropriately designed and installed. Dust should not be able to flow back in the opposite direction, for example, in the event of component failure or airflow failure. The transfer velocity should be sufficient to ensure that dust is carried away and does not settle in the ducting.
- 9.3 The dust extraction points should be positioned in such a way as to prevent dust and powders dropping down from the extract point causing contamination or cross-contamination.
- 9.4 Air should not flow through the dust extraction ducting or return air ducting from the room with the higher pressure to the room with the lower pressure.
- 9.5 Periodic checks should be performed to ensure that there is no build-up of dust in the ducting.
- 9.6 Dust extraction systems should be interlocked, where appropriate, to the relevant AHU to avoid any risk or any impact on pressure cascade imbalances.

10. Protection of the environment

Where exhaust air from equipment such as fluid bed driers, dust extraction systems and facilities carries dust loads, adequate filtration or other control technology should be in place to prevent contamination of the ambient air.

- 10.1 Waste from dust extraction and collection systems should be disposed of in an appropriate manner.
- 10.2 Dust-slurry should be removed by suitable means, for example, a drainage system or waste removal contractor.

11. Commissioning

Note: Commissioning is a precursor to system qualification and validation, and is normally associated with good engineering practice (GEP).

12. Qualification

Note: For general notes on qualification and validation, see *WHO guidelines on validation* (7).

- 12.1 HVAC systems, including recirculation and full fresh air systems, should be qualified to ensure continued performance in accordance with specifications and achievement of the conditions as specified.
- 12.2 The scope and extent of qualification should be determined based on risk management principles.
- 12.3 The qualification of the HVAC system should be described in a master plan. The master plan should define the nature and extent of testing, the test procedures and protocols to be followed.
- 12.4 Where relevant, the procedures followed for conducting the tests should be in accordance with the appropriate parts of the standard as mentioned in ISO 14644 (8) and relevant WHO guidelines.
- 12.5 The design condition, operating ranges, alert and action limits should be defined. Alert limits should be based on system capability.
- 12.6 Performance parameters to be included in qualification of the HVAC system should be determined by means of a risk assessment.
- 12.7 Acceptable tolerances for system parameters, where appropriate, should be specified before commencing the physical installation.

- 12.8 There should be standard operating procedures describing the action to be taken when alert and action limits are reached. This may include, where relevant:
- temperature;
 - relative humidity;
 - supply air quantities;
 - return air or exhaust air quantities;
 - room air-change rates;
 - room pressures and pressure differentials;
 - airflow pattern tests;
 - unidirectional airflow velocities;
 - containment system velocities;
 - HEPA filter penetration tests;
 - room particle count tests;
 - duct leakage tests;
 - materials of construction;
 - microbiological counts;
 - de-dusting and dust extraction systems.
- 12.9 Where routine or periodic revalidation is done, the frequency should be established based on, for example, risk, the type of facility, the level of product protection necessary, performance of the system and the extent of routine ongoing monitoring activities.
- 12.10 Any change to the HVAC system should be handled according to a change control procedure. The extent of qualification or requalification should be decided based on the scope and impact of the change.

13. Maintenance

- 13.1 Operation and maintenance (O&M) manuals, procedures and records should be available and kept up to date with details of any system revisions made.
- 13.2 O&M manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system.
- 13.3 The O&M manuals may typically contain the following information:
- system description;
 - operating instructions;

- troubleshooting;
- commissioning data;
- maintenance instructions;
- list of equipment suppliers;
- spare parts list;
- equipment data/capacity schedules;
- supplier's literature;
- control system description;
- electrical drawings;
- as-built drawings.

13.4 There should be a planned preventive maintenance programme for the HVAC system. The details of this programme should be commensurate with the criticality of the system and components.

13.5 Maintenance activities should not have any negative impact on product quality and should normally be scheduled to take place at appropriate times, for example, outside production hours.

In case of system stoppages, appropriate quality management system procedures should be followed. Where necessary, the root cause and impact should be assessed and appropriate corrective and preventive action taken. Where necessary, qualification or requalification should be considered.

13.6 HEPA filters should be changed by a competent person and this should be followed by installed filter leakage testing.

13.7 Records should be kept for a sufficient period of time.

References and further reading

References

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8. ISO 14644 – Cleanrooms and associated controlled environments package, including ISO 14644-1 to ISO 14644-10 (updated regularly). Geneva: International Standard Organizations.

Further reading

- Good manufacturing practices: quality assurance of pharmaceuticals. WHO guidelines, good practices, related regulatory guidance and GXP training materials. Geneva: World Health Organization (CD-ROM, updated 2016).
- ICH Harmonised tripartite guideline on quality risk management (Q9). Geneva: The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2005.
- Supplementary Guidelines on Good Manufacturing Practices: Validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth report. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/bitstream/handle/10665/43443/WHO_TRS_937_eng.pdf?sequence=1) (under revision).
- WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981; https://iris.who.int/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1&isAllowed=y).
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1.7 Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products

Part 2: Interpretation of *Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products*

Annex 2, WHO Technical Report Series, 1019,
2019

Background

The World Health Organization (WHO) published the first edition of its *Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* in 2006 (1).

Having considered various comments and the recommendations through public consultation over several years, the WHO Expert Committee on Specifications for Pharmaceutical Preparations agreed, during its Fifty-first meeting held in October 2017, that the *Supplementary guidelines for good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* guidelines, as amended, be adopted as Part 1 (2).

It was agreed that Part 1 consists of guidelines that contain recommendations on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile products, and further agreed that Part 1 be supported by an additional document that reflects the interpretation of the recommendations in Part 1.

This document is Part 2 and will be considered for adoption as such after consultation.

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1. Introduction and scope

This document represents Part 2 of the guidelines for good manufacturing practices (GMP) for heating, ventilation and air-conditioning (HVAC) systems. It contains non-binding examples, drawings, technical representations and interpretation in support of Part 1 of the HVAC systems guidelines (2).

It is intended to be a basic and explanatory guide for use by pharmaceutical manufacturers and GMP inspectors. It is not intended to be prescriptive in specifying requirements and design parameters but it attempts to facilitate a harmonized understanding of expectations for HVAC systems for manufacturers and regulators of non-sterile products.

Part 1 and Part 2 focus on good practices for HVAC systems for non-sterile products. Where applicable, some of the principles referred to may be considered in the HVAC design and approach for other dosage forms. These two documents are, however, not intended to be used as criteria for the design or review of HVAC systems for, for example, active pharmaceutical ingredients or sterile products.

Other relevant national and international standards, as applicable, should be considered when Part 1 and Part 2 are used. These include, but are not limited to, current publications such as ISO 14644 (3) and American Society of Heating and Air-Conditioning Engineers (ASHRAE) standards.

In general, HVAC systems can play an important role in facilitating a suitable environment for the manufacture of quality pharmaceutical products. Therefore, careful consideration should be given to their design. When designing an HVAC system, careful consideration should also be given to the building design and layout of areas, as these may influence the decision and design relating to, for example, the number of air-handling units (AHUs), components in AHUs, room pressure, pressure differentials, pressure cascades, levels of filtration, humidification, dehumidification, and heating and cooling of air. These may, in turn, have an impact on the quality of materials and products, as well as the functioning of equipment and instruments.

The conditions of areas should be defined and should be appropriate for storage, manufacture and use, as appropriate, of equipment, instruments, materials and products. It should further ensure that comfortable conditions are maintained for operators.

2. Risk assessment and design

2.1 Risk assessment

In line with the current approach in GMP, risk identification should be done for utilities such as HVAC systems. A science-based, comprehensive exercise of risk assessment should be used to determine risks related to possible failure of the HVAC system and AHUs (including their components and subcomponents). An appropriate risk-

assessment tool, such as failure modes and effects analysis or fault tree analysis, should be selected. Controls should be identified to eliminate the risks, or minimize the risk to an acceptable level. For example, the effect of failure of one or more AHUs in the HVAC system; failure of dust-extraction systems; or failure of AHU components such as filters, heating coils, cooling coils and fans should be assessed, and appropriate controls should be identified and implemented.

For more information on risk assessment, refer to the current WHO [World Health Organization] *guidelines on quality risk management* (4).

2.2 Design parameters

Manufacturers should define the design parameters of the HVAC system, to ensure appropriate operation and functioning of the system, which is needed for all the areas. Special consideration should be given to the required conditions for storage, manufacture and handling of materials and products, equipment and instrument functioning, personnel (operator) requirements and contamination control.

3. Glossary

For definitions and abbreviations, see Part 1 (2).

4. Premises

4.1 Premises design

Both the architectural design of the building and that of the HVAC system should be carefully considered when attempting to achieve the general objectives of preventing contamination and cross-contamination and ensuring an appropriate environment for the production and control of pharmaceutical products. It is important to ensure that the required environmental conditions, cleanliness and containment are achieved and maintained.

The infiltration of contamination from outside air should be minimized by the use of appropriate filtration, room pressure differentials and airlocks. Manufacturing facilities should normally be maintained at a positive pressure relative to the outside, to limit the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to the ambient pressure, special precautions should be taken to avoid ingress and egress of contaminant.

Risks of contamination should be controlled, especially in the case of potent contaminants, to ensure protection of materials, products, operators and the environment.

Where necessary, air locks, change rooms and pass-through hatches may be considered and provided with effective ventilation and filtered air. Special attention

should be given to door design, as gaps between doors and floors, doors opening into low-pressure areas, and sliding doors can result in changes in the pressure differential between areas. An interlocking system and a visual and/or audible warning system may be used, where required, to prevent opening of more than one door at a time where required.

In addition to the design of the premises, general controls should be in place to ensure protection of materials, products and personnel. The HVAC system can play a role in achieving this objective. Where identified, areas should be maintained within defined limits for temperature, relative humidity, and viable and non-viable particles. To ensure that the clean area is maintained at the defined limits, areas are normally classified. When classifying the area, the manufacturer should state whether the classification is for the “as built”, “at rest” or “in operation” condition. For details, including definitions, see ISO 14644 (3).

Manufacturers may use different terms when classifying areas, including Grade A, B, C, D, or ISO 7, ISO 8, or Level 1, Level 2 or others (5) (see Table A2.1). When classifying an area, the class selected should be defined and described (see also Section 7).

**Table A2.1
Examples of area classification (5)**

Level	Example of area
Level 1	General area with normal housekeeping and maintenance, where there is no potential for product contamination, e.g. warehousing
Level 2	Protected area in which steps are taken to protect the pharmaceutical starting material or product from direct or indirect contamination or degradation, e.g. secondary packing, warehousing, first-stage change rooms
Level 3	Controlled area in which specific environmental conditions are defined, controlled and monitored, to prevent contamination or degradation of the pharmaceutical starting material or product, e.g. where product, starting materials and components are exposed to the room environment; plus equipment wash and storage areas for equipment product contact parts

The following describes approaches (with illustrations by means of diagrams) of different room arrangements and room pressures.

4.2 Weighing/dispensing and sampling areas

A room for weighing (e.g. dispensing of materials) should be of appropriate design (for examples, see Figs A2.1 and A2.2). It is often advantageous to have several rooms associated with the weighing activity. These may include a pre-weighing staging area, personnel airlock, material airlock, weighing area with a containment booth, post-

weighing staging area, washing area and provision for waste removal. The HVAC system for such areas should ensure that the areas have at least the same area classification as other production areas where materials and products are exposed to the environment, logical flow of material and personnel, and an appropriate number of AHUs, as well as appropriate pressure differentials, containment, dust control, and rate of air exchange.

The objective of having a booth in a weighing room is to provide dust containment and operator protection. For example, the dust generated at the weighing location should be extracted through a perforated worktop, thus protecting the operator from dust inhalation, but at the same time protecting the material and product from contamination by the operator by means of the vertical airflow stream. The airflow velocity should be such that it does not disrupt the sensitivity of balances.

Fig. A2.1
Example of a weighing area

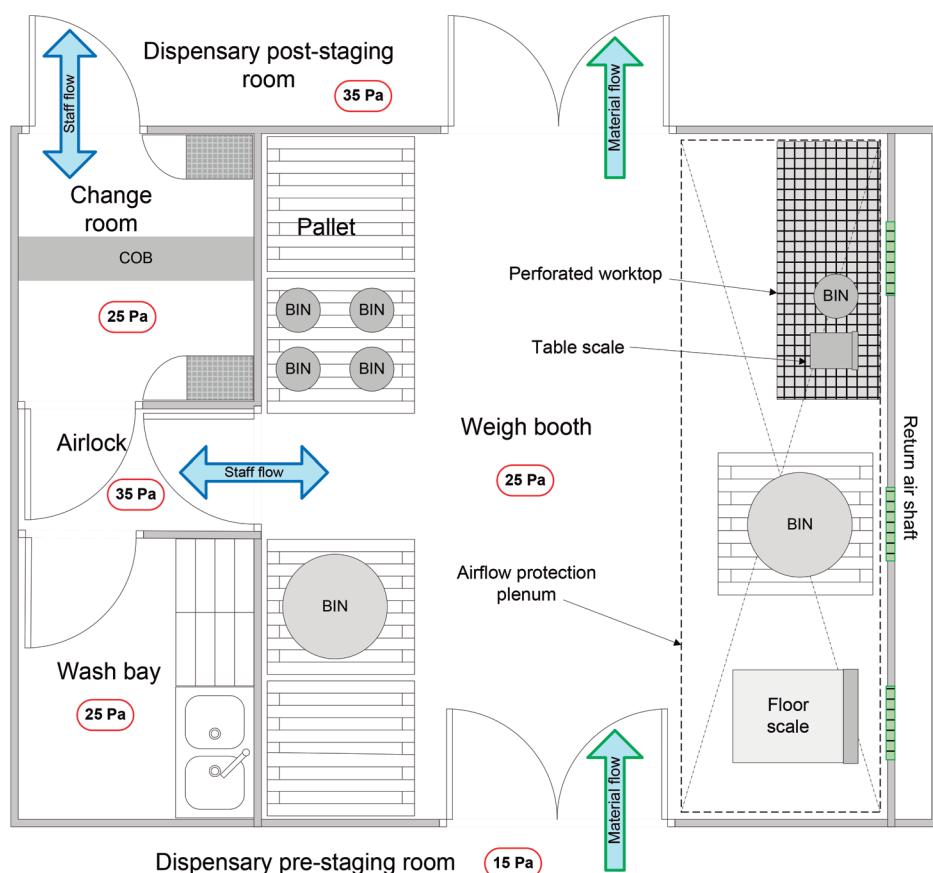


Fig. A2.2
Examples of weighing areas

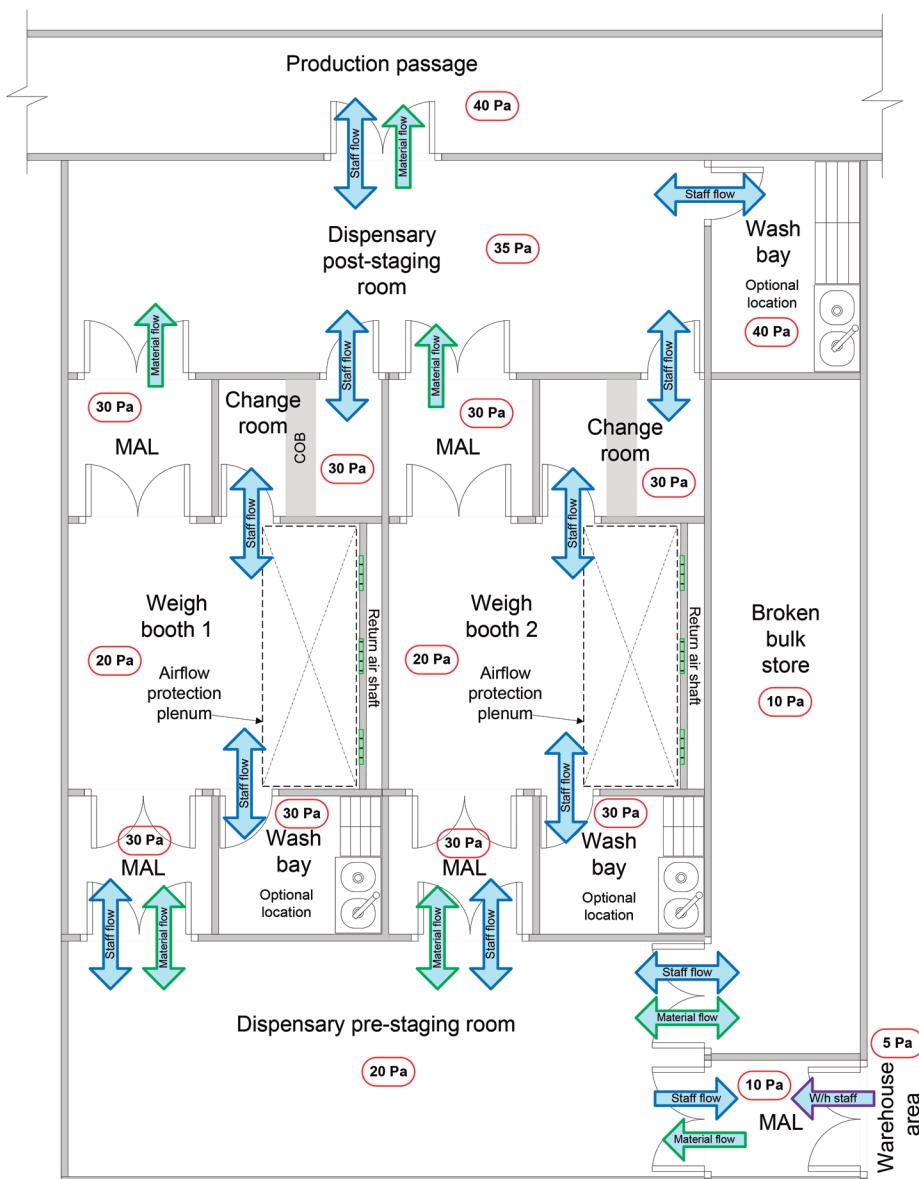
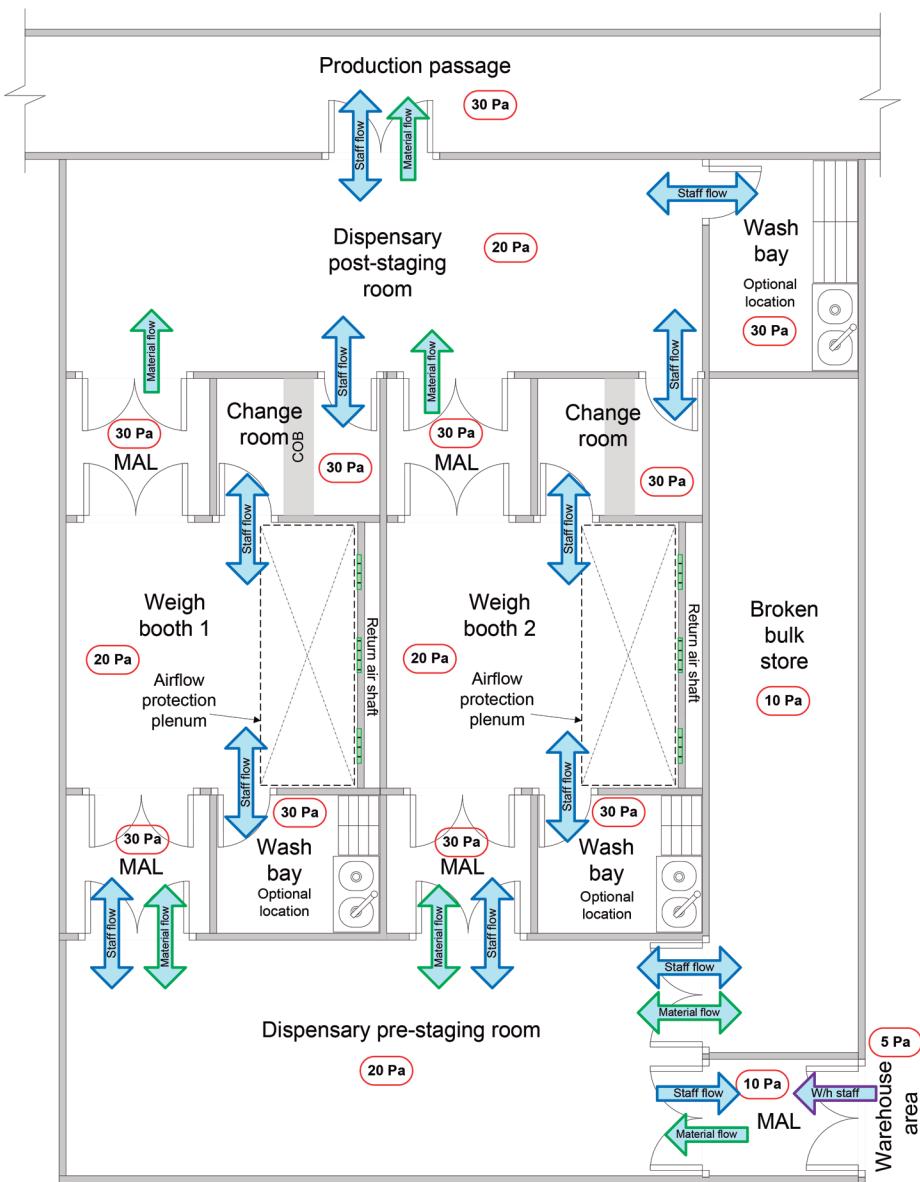


Fig A2.2 continued



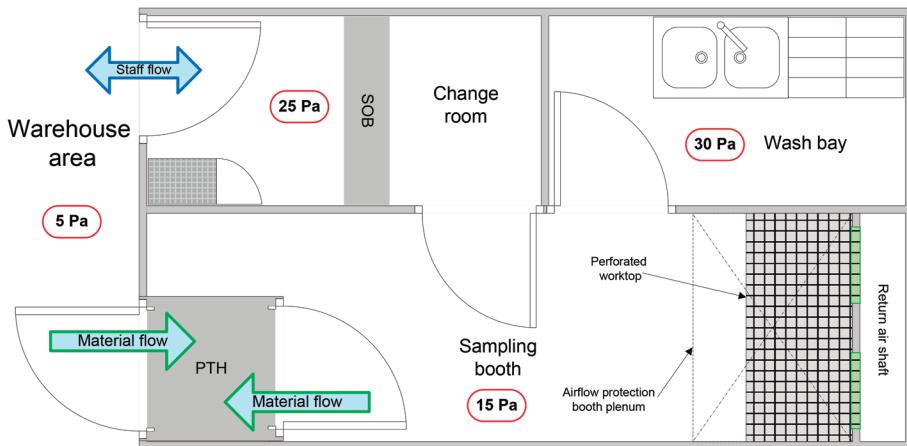
Note that the adjacent room pressures impact on determining the dispensary pressures.

COB: cross-over bench; MAL: material airlock; W/h: warehouse.

Similar aspects may be considered when designing a sampling area, as materials and primary components may be exposed to the environment during sampling (for examples, see Figs A2.3 and A2.4).

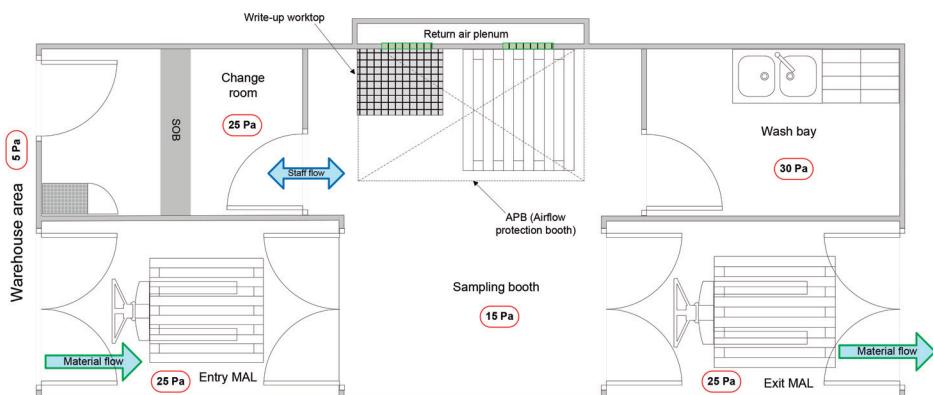
Sampling of materials such as starting materials, primary packaging materials and products, should be carried out in the same environmental conditions that are required for further processing of the product.

Fig. A2.3
Example of a sampling area



PTH: pass-through hatch.

Fig. A2.4
Example of a sampling area



MAL: material airlock.

A clean corridor concept is usually recommended for non-sterile oral solid-dosage form production areas, where there is then a higher pressure in the corridor compared to airlocks or production rooms. This is to facilitate containment of dust and contaminants that may have been generated in production rooms (see also the principles mentioned in the text on weighing/dispensing and sampling areas) (for an example, see Fig. A2.5).

To further support containment, consideration may also be given to having material airlocks (MALs) and personnel airlocks (PALs), where needed, for entry and exit of processing areas (for an example, see Fig. A2.6). Appropriately designed airlocks can assist in ensuring containment. Additional controls, such as pressure differentials between areas, an appropriate number of air changes in an area, and sufficient filtration of air, should be in place. The use of airlocks assists in ensuring containment; however, other means may be considered to achieve this objective, such as closed systems and pressure gradients between adjacent areas.

Fig. A2.5
Example of a change room and some production areas

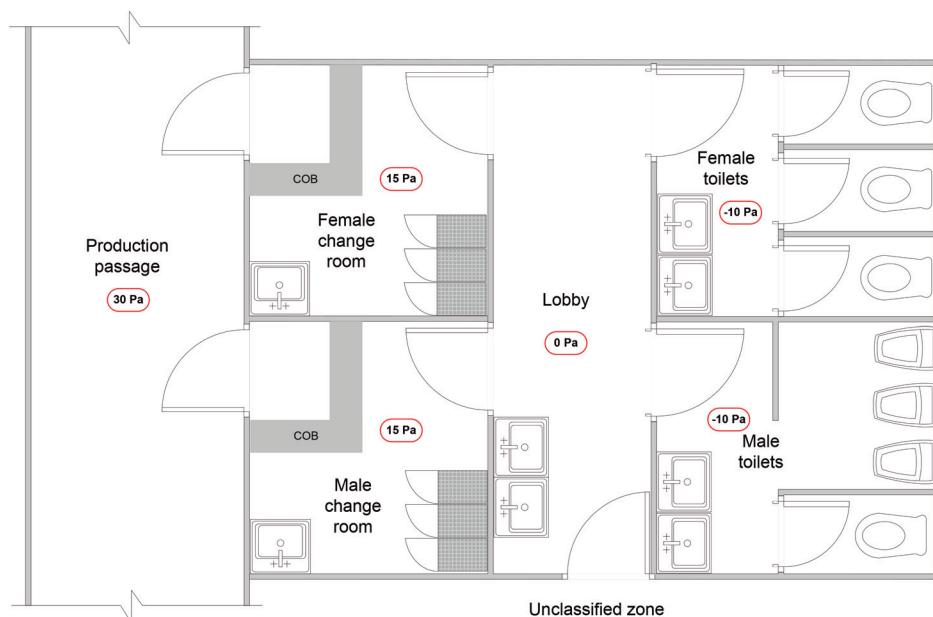
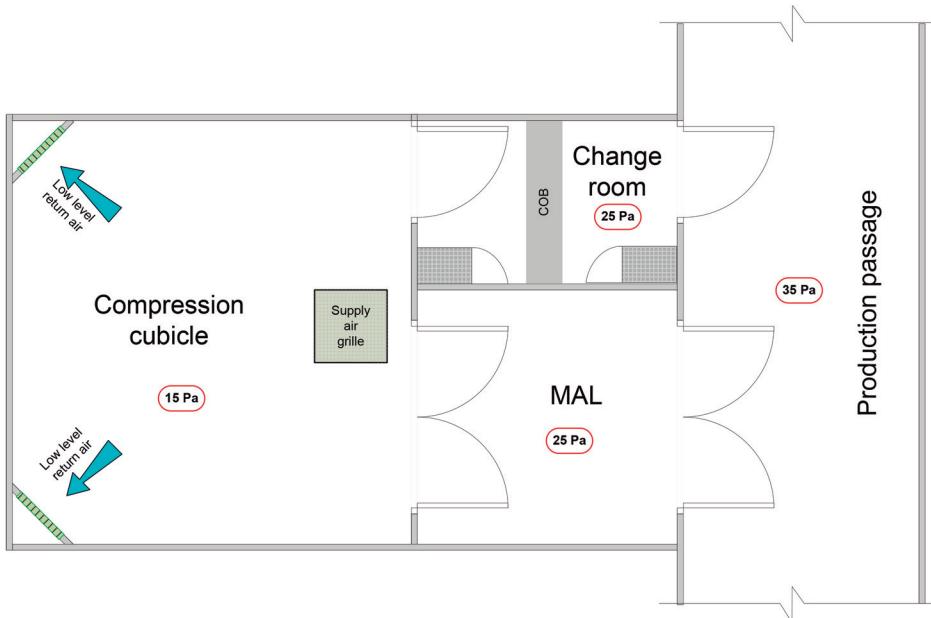


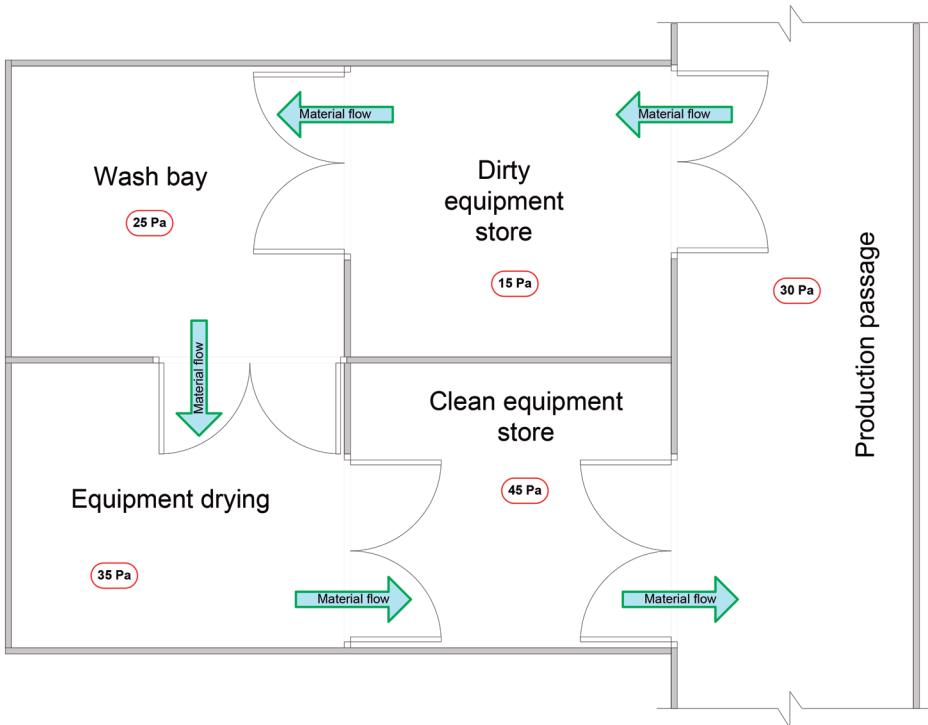
Fig. A2.6

Example of a compression cubicle with material (MAL) and personnel (PAL) airlocks (also used as an area to change garments)



Washing areas should be designed and used in such a manner that equipment and components will not be re-contaminated after cleaning. The system supplying and extracting air from the area(s) should be suitably designed to ensure that this objective is achieved. Principles that may be considered include (but are not limited to) filtration of air, pressure differentials between areas, air changes per hour and airflow directions (for an example, see Fig. A2.7).

Fig. A2.7
Example of a washing area



5. Design of HVAC systems and components

The HVAC system should be appropriately designed, taking into consideration the design of the facility, with various rooms or areas for storage of materials and in-process materials or products, processing, and movement of materials, products and personnel. The required cleanliness classification should be achieved, as well as other parameters, such as air filtration, airflow velocity, air volumes, pressure differentials, temperature, relative humidity, viable and non-viable particle counts and containment. Conditions and limits should be specified, based on need. Manufacturers should determine and define limits for these. These should be realistic, appropriate and scientifically justifiable at rest, in operation and as built at the time of design. In determining these, relevant factors and risks should be considered, including but not limited to possible failures of AHUs, seasonal variations, properties and types of materials and products, numbers of personnel and risks of cross-contamination.

Other aspects, such as the number of AHUs, dust-collecting or dust-extraction systems, the need for recirculation of air, percentage of fresh air (in the case of

recirculated air) and the level of filtration of air should be defined by the manufacturer when considering the design of the facility and activities in different areas and rooms.

Manufacturers should maintain schematic drawings of the HVAC system, AHUs and components. These should reflect the initial design and installation, as well as the current situation. Changes made during the life-cycle of the system should be reflected in change-control records and qualification protocols and reports, as appropriate.

The components selected in an HVAC system should be of sufficient capacity to ensure that the design objectives are met (e.g. for heating, cooling, humidification, dehumidification, airflow volumes), taking impacting factors into consideration, such as loss of air due to leakage and seasonal variations. Materials for construction of components, and their placement, should be such that these do not become the source of contamination. For example, components should not shed particles and the sequence of components should be logical; for example, filters should be placed in such a manner that any possible contaminants generated in the system can be retained by filters and not be introduced into the production area.

To prevent contamination of areas, components such as ventilation dampers, filters and other services should be accessible from outside the manufacturing areas (such as service corridors).

The overall design should be such that there is no possibility of undesired, unfiltered air or contaminants entering manufacturing areas.

5.1 Containment

Manufacturers should ensure that appropriate measures are taken to contain product dust in a manufacturing area, thus preventing or minimizing the risk of contamination of other areas and possible cross-contamination. In some cases, it may be advisable to have airlocks or pass-through hatches between rooms or areas. In addition, sufficient dilution, pressure differentials (recommended minimum values of 5 Pa) and airflow directions can further support containment in an area.

5.2 Cleanliness

Areas should be maintained at the defined levels of cleanliness and classifications. The HVAC system can support this through, for example, appropriate levels of filtration of air, dilution and dust removal. Equipment, containers, personnel and other related components should be appropriately located or placed in areas so as not to obstruct airflow and the effectiveness of the HVAC system.

Recontamination should be prevented by ensuring that movement of material and personnel is within the same area classification and not back and forth between areas of different classification. Where such back-and-forth movement is unavoidable, appropriate controls should be identified and implemented, to ensure that moving from a higher class to a lower-classified area and back to a higher-classified area will not result in contaminants being brought into the cleaner classified area.

5.3 Automated monitoring systems

The performance of the HVAC system achieving and maintaining the desired results for parameters such as temperature, relative humidity, airflow and pressure differential should be carefully controlled and monitored. This is to ensure that there is no departure from these limits during manufacturing. Monitoring systems should be in place to ensure that the system operates within its design limits. Manual or automated (computerized) systems may be used.

Automated monitoring systems may provide possibilities for ongoing monitoring with better assurance of compliance with the defined limits. Where these automated systems are considered to be good practice (GXP) systems, these should be appropriately validated. The scope and extent of validation of the computerized system should be determined, justifiable and appropriately executed. This includes, but is not limited to, access and privileges to the software, setting of limits, monitoring and acknowledging alarms, audit trails, controls, and reporting.

5.4 Switching off air-handling units

It is recommended that the HVAC system be operational on an ongoing basis. Where a manufacturer decides to use energy-saving modes or switch some selected AHUs off at specified intervals, such as overnight, at weekends or for extended periods of time, care should be taken to ensure that materials and products are not affected. In such cases, the decision, procedures and records should be sufficiently documented and should include risk assessment, standard operating procedures, records and validation. This includes procedures and records for the start-up and shut-down sequence of AHUs.

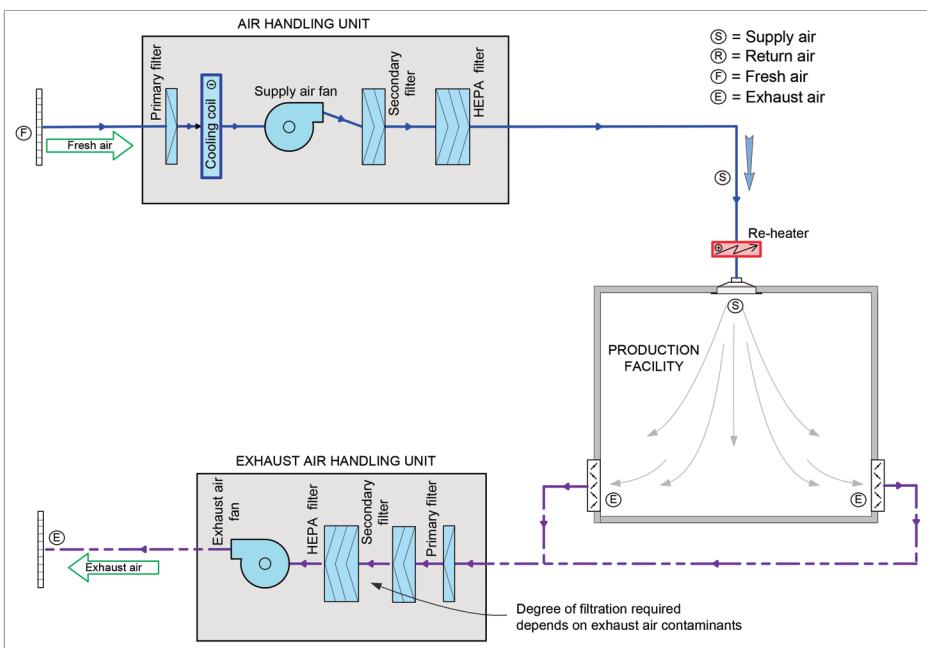
6. Full fresh air systems and recirculation systems

Manufacturers may select to have full fresh air systems (for an example, see Fig. A2.8) or recirculate treated air supplied to production areas (in a full fresh air system, no air is recirculated; in recirculation systems, a defined percentage of the air is recirculated). In both cases, the air supplied to the production areas should be appropriately treated, to ensure that the environmental conditions specified are met and that the risks for contamination and cross-contamination are controlled.

Manufacturers using recirculation systems should determine the percentage of fresh air to be supplied to the relevant manufacturing areas, as required by national and international standards. This volume of air should be verified during qualification.

In both scenarios, appropriate levels of filtration should be applied, to prevent contamination and cross-contamination. Manufacturers should ensure that when high-efficiency particulate air (HEPA) filters are used, these are appropriately installed, not damaged and thus suitable for the intended use (see tests described in Section 12).

Fig. A2.8
Example of a full fresh air system



HEPA: high-efficiency particulate air filter.

7. Air filtration, airflow direction and pressure differentials

Effective ventilation and appropriate levels of filtration are recommended in basic GMP guidelines. Manufacturers should determine which classes of filters should be used in ensuring that contaminants from outside are not introduced into manufacturing areas and that where recirculation systems are used, filtration of recirculated air is carried out effectively, to ensure that there is no risk of cross-contamination. Where different products are manufactured in different rooms in the same facility at the same time, appropriate controls should be in place to ensure containment and prevention of contamination and cross-contamination.

Filters selected for air filtration should be determined and specified. When a manufacturer chooses to install HEPA filters to achieve the desired degree of filtration of air, these filters may be placed in the AHU, or may be installed terminally near the supply grille.

Filters have an impact on the cleanroom class or level of protection. The different levels of protection and recommended filter grades are presented in Table A2.2.

Table A2.2
Levels of protection and recommended filtration (5)

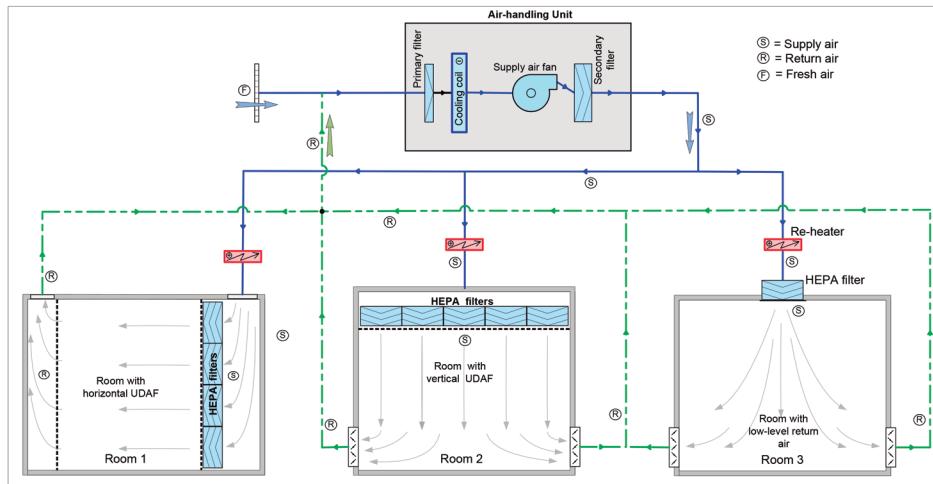
Level of protection	Recommended filtration
Level 1	Primary filters only (e.g. EN 779 G4 filters)
Level 2	Protected areas operating on 100% outside air: primary plus secondary filters (e.g. EN 779 G4 plus F8 or F9 filters)
Level 3	Production facility operating on recirculated plus ambient air, where potential for cross-contamination exists: primary plus secondary plus tertiary filters (e.g. EN 779 G4 plus F8 plus EN 1822 H13 filters; for full fresh air system, without recirculation, G4 and F8 or F9 filters are acceptable)

The number of air changes or air-exchange rates should be sufficient. A guidance value is between 6 and 20 air changes per hour. Manufacturers should also establish how much time it takes for a room that is out of its classification to return within the specified class. This is often referred to as clean-up or recovery time. A guidance time period for clean-up or recovery is about 15–20 minutes.

Airflow directions should be specified and proven to promote containment and not be adversely affected or obstructed by equipment, utilities, containers or personnel. The location of supply and return or exhaust air grilles should facilitate appropriate airflow directions in an area.

Fig. A2.9 is a schematic diagram of an example of an air-handling system serving rooms with horizontal directional flow, vertical directional flow and turbulent flow, for rooms 3, 4 and 5, respectively. In these rooms, the HEPA filters are indicated to have been placed terminally mounted in the rooms and not in the AHU. Whenever HEPA filters are terminally mounted, it can assist with preventing cross-contamination from room to room in the event of a fan failure.

Fig. A2.9

Example of horizontal airflow, vertical flow and turbulent flow

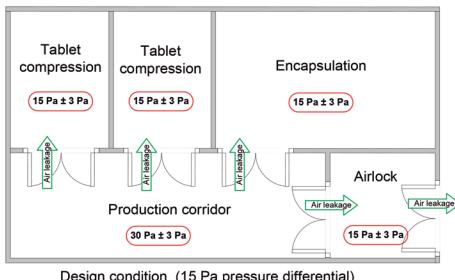
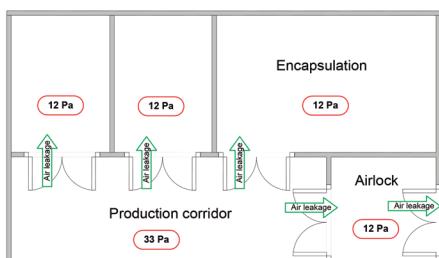
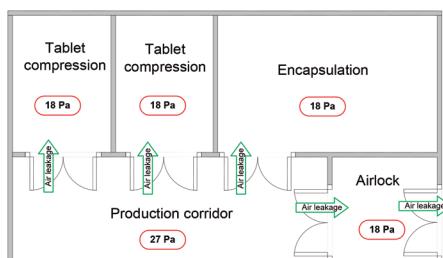
UDAF: unidirectional airflow.

The pressure differential should be of sufficient magnitude to ensure containment and prevention of flow reversal, but should not be so high as to create turbulence problems. It is suggested that pressure differentials of between 5 Pa and 20 Pa be considered. Where the design pressure differential is too low and tolerances are at opposite extremities, a flow reversal can take place. There should be no risk of overlap in the acceptable operating range, for example, 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in failure of the pressure cascade (for examples, see Fig. A2.10). The upper and lower limits for pressure differentials between areas in a facility should be defined by the manufacturer. Where there are interleading rooms, the limits should be appropriate to ensure that there is no overlap in actual values, as this may result in loss in pressure differential between areas and even reversal of air flow.

Cumulative tolerances for the instruments measuring pressure differential should not cause a situation where an undetected reversal of airflow is possible. This can be accomplished by setting the limits such that there is no overlap in the differential between adjacent rooms at the extremes of acceptable tolerances, or by using a common reference point such as the corridor outside of a suite of rooms.

The pressure control and monitoring devices used should be calibrated and, where possible, be linked to an alarm system set according to the determined levels.

Fig. A2.10
Examples of pressure cascades

Design condition (15 Pa pressure differential)Image of room pressure gauge
indicating colour-coded normal,
alert & action parametersMaximum differential (21 Pa pressure differential)Minimum differential (9 Pa pressure differential)

7.1 Airlocks

Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock:

- *cascade airlock*: higher pressure on one side of the airlock and lower pressure on the other (for an example, see Fig. A2.11);
- *sink airlock*: lower pressure inside the airlock and higher pressure on both outer sides (for an example, see Fig. A2.12);
- *bubble airlock*: higher pressure inside the airlock and lower pressure on both outer sides (for an example, see Fig. A2.13).

Fig. A2.11

Example of a cascade airlock: in most cases, the internal pressure of the airlock is not critical; the pressure differential between the two outer sides is the important criterion

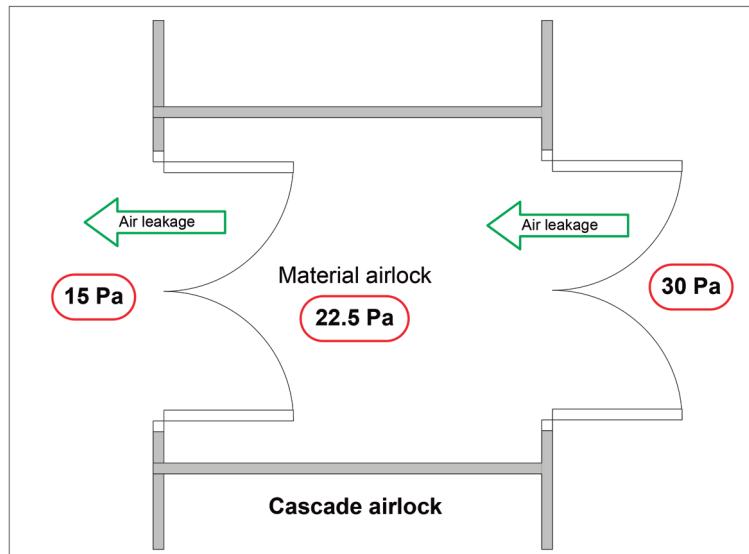


Fig. A2.12

Example of a sink airlock

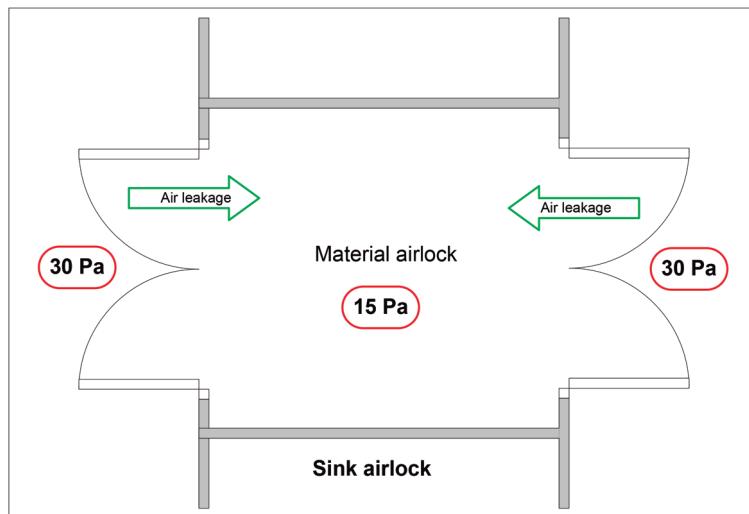
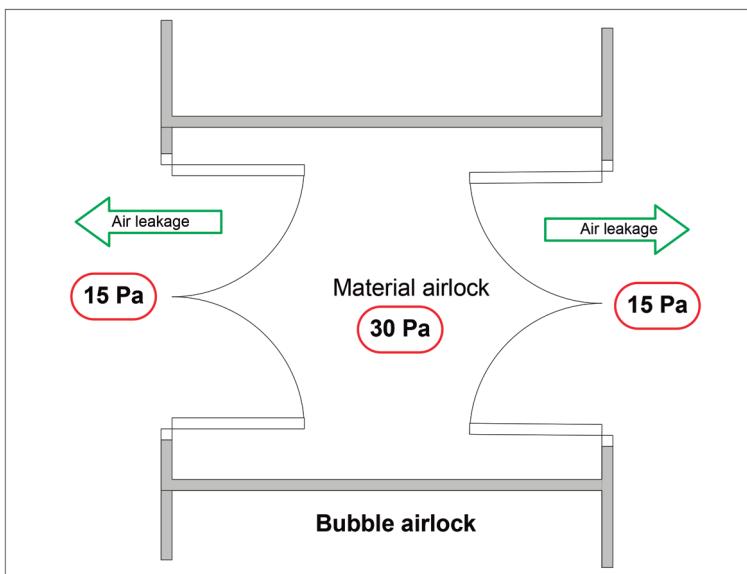


Fig. A2.13
Example of a bubble airlock



Note: The diagrams above and the differential pressures shown here are for illustration purposes only. Pressures indicated in these examples are absolute pressures, whereas the local pressure indication would most likely be the pressure differential from room to room.

Additional controls should be identified through risk identification and risk assessment. For example, where possible, personnel should not move between different areas during production (such as compression rooms and in process control laboratories), unless there is no risk of contamination of other areas. Personnel often become sources of contamination, as they may carry dust from one area to another. Controls may include airlocks or gowning procedures.

8. Temperature and relative humidity

Manufacturers should set appropriate upper and lower limits for temperature and relative humidity for different areas. The required storage conditions specified for the materials and products should be considered when the limits are defined. The HVAC system should be designed in such a manner that these limits can be achieved and maintained through all seasons.

Systems for dehumidification or humidification require special considerations, owing to their contamination risk (e.g. condensate formation, bacterial and fungal contamination, contaminated steam and risks when using mobile systems between

different areas). Chemicals such as corrosion inhibitors or chelating agents, which could have a detrimental effect on the product, should not be added to the boiler system. Humidification systems should be well drained. No condensate should accumulate in air-handling systems. Other humidification appliances such as evaporative systems, atomizers and water mist sprays, should not be used, because of the potential risk of microbial contamination. Air filters should not be installed immediately downstream of humidifiers, as moisture on the filters could lead to bacterial growth. Cold surfaces should be insulated to prevent condensation within the clean area or on air-handling components. Chemical driers using silica gel or lithium chloride are acceptable, provided they do not become sources of contamination.

9. Dust, vapour and fume control

Manufacturers should ensure that dust-generated vapours and fumes are effectively removed from the manufacturing areas. Extraction or collecting systems should be designed and qualified to demonstrate this. Sufficient air velocity should be maintained in such systems to effectively remove dust and vapours.

A dust extractor should normally not serve different rooms where different products can be processed at the same time, owing to the risks such as backflow or flow from room to room, resulting in possible contamination and cross-contamination.

Wherever possible, dust or vapour contamination should be removed at source, that is, as close as possible to the point where the dust is generated. Ducting for dust extraction should be designed with sufficient transfer velocity (determined by the manufacturer, depending on materials and products processed), to ensure that dust is carried away, and does not settle in the ducting (a guidance value is 15–20 m/s). As vapours can be problematic, extraction may be supported by directional airflow to assist in the removal. The density of the vapour should be taken into consideration, with extract grilles at a high level or possibly at both high and low levels.

10. Protection of the environment

Manufacturers should have controls in place to ensure that air from production areas, including contaminated air from equipment such as fluid bed driers, is passed through appropriate levels of filtration, to ensure that the environment is not polluted. Manufacturers should consult national and international environmental legislation.

11. Commissioning

Where manufacturers perform commissioning, this should be clearly documented.

12. Qualification

Manufacturers should consider all stages of qualification for their HVAC systems. This includes, where appropriate, user requirement specification, design qualification, factory acceptance test, site acceptance test, installation qualification, operational qualification and performance qualification. Qualification to be done over the life-cycle of the HVAC system should be described and executed, including, for example, when changes are made to the system.

Validation master plan(s), protocols, reports and source data for tests should be available. The scope and extent of qualification should be determined based on risk assessment. Parameters with limits included in qualification (such as temperature test, airflow direction, viable and non-viable particle counts) should be justified by manufacturers. The procedures followed for the performance of the tests should generally be in line with the standard as described in ISO 14644 (3).

Some of the typical HVAC system parameters that should be included in the tests during qualification are listed next and the selection of the parameters should be justified (for examples, see Table A2.3). It is recommended that the tests be done at defined intervals. The tests typically cover:

- temperature;
- relative humidity;
- supply air quantities;
- return air or exhaust air quantities;
- room air-change rates;
- room pressures and pressure differentials;
- airflow pattern tests;
- unidirectional airflow velocities;
- containment system velocities;
- HEPA filter penetration tests;
- room particle count tests;
- duct leakage tests;
- materials of construction;
- microbiological counts;
- de-dusting and dust extraction systems.

Table A2.3
Considerations for test parameters and procedures

Test parameter	Test procedure	Note
Temperature	ISO 14644 (3) and WHO Technical Report Series, No. 961 (6)	Adapt ISO tests in case of longer periods, and consider the temperature mapping test as described in WHO Technical Report Series
Relative humidity	ISO 14644 (3) and WHO Technical Report Series, No. 961 (6)	Adapt ISO tests in case of longer periods, and consider the temperature mapping test as described in WHO Technical Report Series
Pressure differential	ISO 14644 (3)	Consider extended periods to show consistency in performance
Airflow volumes	ISO 14644 (3)	
Installed filter leakage	ISO 14644 (3)	
Particle counts	ISO 14644 (3)	
Airflow direction	ISO 14644 (3) or company procedure (smoke test)	Ensure a continuous capture of the process, e.g. video, with correct angles to demonstrate air flow direction, and appropriate records and labelling indicating date, time, signatures and area filmed and recorded in a traceable manner
Airflow velocity	ISO 14644 (3)	
Recovery	In-house procedure	
Air-change rate		

13. Maintenance

Manufacturers should maintain current documentation for HVAC systems, including operation and maintenance manuals, schematic drawings, procedures and records. Repairs, maintenance and preventive maintenance (including cleaning, replacement of components, changes, qualification) should be executed in accordance with procedures. Records for these should be maintained for an appropriate time.

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2. WHO good manufacturing practices: starting materials

2.1 WHO good manufacturing practices for active pharmaceutical ingredients (bulk drug substances)

Annex 2, WHO Technical Report Series, 957,
2010

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This text is based on the International Conference on Harmonisation (ICH) Q7: *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*. November 2000.

1. Introduction

1.1 Objective

This document (guide) is intended to provide guidance regarding good manufacturing practices (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

In this guide “manufacturing” is defined to include all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and the related controls. In this guide the term “should” indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance. For the purposes of this guide, the terms “current good manufacturing practices” and “good manufacturing practices” are equivalent.

The guide as a whole does not cover safety aspects for the personnel engaged in the manufacture, nor aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

This guide is not intended to define registration and filing requirements or modify pharmacopoeial requirements. This guide does not affect the ability of the responsible regulatory agency to establish specific registration or filing requirements regarding APIs within the context of marketing or manufacturing authorizations or pharmaceutical applications. All commitments in registration and filing documents must be met.

1.2 Regulatory applicability

Within the world community, materials may vary as to the legal classification as an API. When a material is classified as an API in the region or country in which it is manufactured or used in a pharmaceutical product, it should be manufactured according to this guide.

1.3 Scope

This guide applies to the manufacture of APIs for use in finished pharmaceutical products (FPPs). It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance, but should be performed in accordance with GMP guidelines for FPPs as defined by local authorities.

This guide covers APIs that are manufactured by chemical synthesis, extraction, cell culture or fermentation, by recovery from natural sources, or by any combination of these processes.

Specific guidance for APIs manufactured by cell culture or fermentation is described in section 18.

This guide excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it does include APIs that are produced using blood or plasma as raw materials. Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this guide. In addition, the guide does not apply to medical gases, bulk-packaged FPPs, and manufacturing and control aspects specific to radiopharmaceuticals.

Section 19 contains guidance that only applies to the manufacture of APIs used in the production of FPPs specifically for clinical trials (investigational medicinal products).

An “API starting material” is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in house.

API starting materials normally have defined chemical properties and structure. The company should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which “API starting materials” are entered into the process. For other processes (e.g. fermentation, extraction or purification), this rationale should be established on a case-by-case basis.

Table 1 gives guidance on the point at which the API starting material is normally introduced into the process. From this point on, appropriate GMP as defined in this guide should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical.

The guidance in this document would normally be applied to the steps shown in grey in Table 1. It does not imply that all steps shown should be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification and packaging. Physical processing of APIs, such as granulation, coating or physical manipulation of particle size (e.g. milling and micronizing), should be conducted at least to the standards of this guide.

This GMP guide does not apply to steps prior to the introduction of the defined “API starting material”.

Table 1^a
Application of this guide to API manufacturing

Type of manufacturing	Application of this guide to steps (shown in grey) used in this type of manufacturing				
Chemical manufacturing	Production of the API starting material	Introduction of the API starting material into process	Production of intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plants	Cutting and initial extraction(s)	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/communuting			Physical processing, and packaging
Biotechnology: fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
“Classical” fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

^a This table has been taken from the ICH Harmonised Tripartite Guideline: Active Pharmaceutical Ingredients Q7. Current Step 4 version, dated 10 November 2000.



Increasing GMP requirements

2. Quality management

2.1 Principles¹

- 2.10 Quality should be the responsibility of all persons involved in manufacturing.
- 2.11 Each manufacturer should establish, document and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.
- 2.12 The system for managing quality should encompass the organizational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality-related activities should be defined and documented.
- 2.13 There should be a quality unit(s) that is independent of production and that fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.
- 2.14 The persons authorized to release intermediates and APIs should be specified.
- 2.15 All quality-related activities should be recorded at the time they are performed.
- 2.16 Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.
- 2.17 No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine as described in section 10.20 or the use of raw materials or intermediates pending completion of evaluation).
- 2.18 Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g. quality related complaints, recalls and regulatory actions).

2.2 Responsibilities of the quality unit(s)

- 2.20 The quality unit(s) should be involved in all quality-related matters.
- 2.21 The quality unit(s) should review and approve all appropriate qualityrelated documents.

¹ This system of numbering sections is different to the usual WHO style. It is used here to harmonize with the guide used in inspection reports internationally.

2.22 The main responsibilities of the independent quality unit(s) should not be delegated.

These responsibilities should be described in writing and should include but not necessarily be limited to:

1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company.
2. Establishing a system to release or reject raw materials, intermediates, packaging and labelling materials.
3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution.
4. Making sure that critical deviations are investigated and resolved.
5. Approving all specifications and master production instructions.
6. Approving all procedures impacting the quality of intermediates or APIs.
7. Making sure that internal audits (self-inspections) are performed.
8. Approving intermediate and API contract manufacturers.
9. Approving changes that potentially impact quality of intermediates or APIs.
10. Reviewing and approving validation protocols and reports.
11. Making sure that quality-related complaints are investigated and resolved.
12. Making sure that effective systems are used for maintaining and calibrating critical equipment.
13. Making sure that materials are appropriately tested and the results are reported.
14. Making sure that there are stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate.
15. Performing product quality reviews (as defined in section 2.5).

2.3 Responsibility for production activities

The responsibility for production activities should be described in writing, and should include but not necessarily be limited to:

1. Preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures.
2. Producing APIs and, when appropriate, intermediates according to preapproved instructions.
3. Reviewing all production batch records and ensuring that these are completed and signed.

4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded.
5. Making sure that production facilities are clean and when appropriate disinfected.
6. Making sure that the necessary calibrations are performed and records kept.
7. Making sure that the premises and equipment are maintained and records kept.
8. Making sure that validation protocols and reports are reviewed and approved.
9. Evaluating proposed changes in product, process or equipment.
10. Making sure that new and, when appropriate, modified facilities and equipment are qualified.

2.4 Internal audits (self-inspection)

- 2.40 In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.
- 2.41 Audit findings and corrective actions should be documented and brought to the attention of the responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

2.5 Product quality review

- 2.50 Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least a review of:

- critical in-process control and critical API test results;
- all batches that failed to meet established specification(s);
- all critical deviations or non-conformances and related investigations;
- any changes carried out to the processes or analytical methods;
- results of the stability monitoring programme;
- quality-related returns, complaints and recalls; and
- adequacy of corrective actions.

- 2.51 The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

3. Personnel

3.1 Personnel qualifications

- 3.10 There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.
- 3.11 The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.
- 3.12 Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs, and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

3.2 Personnel hygiene

- 3.20 Personnel should practice good sanitation and health habits.
- 3.21 Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand and arm coverings, should be worn when necessary, to protect intermediates and APIs from contamination.
- 3.22 Personnel should avoid direct contact with intermediates or APIs.
- 3.23 Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.
- 3.24 Personnel with an infectious disease or who have open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where their health condition could adversely affect the quality of the APIs, until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

3.3 Consultants

- 3.30 Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

3.31 Records should be maintained stating the name, address, qualifications and type of service provided by these consultants.

4. Buildings and facilities

4.1 Design and construction

4.10 Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.

4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

4.12 Where the equipment itself (e.g. closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

4.13 The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

4.14 There should be defined areas or other control systems for the following activities:

- receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection;
- quarantine before release or rejection of intermediates and APIs;
- sampling of intermediates and APIs;
- holding rejected materials before further disposition (e.g. return, reprocessing or destruction);
- storage of released materials;
- production operations;
- packaging and labelling operations; and
- laboratory operations.

4.15 Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single-use towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

4.16 Laboratory areas and operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.

4.2 Utilities

- 4.20 All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.
- 4.21 Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.
- 4.22 If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.
- 4.23 Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.
- 4.24 Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

4.3 Water

- 4.30 Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.
- 4.31 Unless otherwise justified, process water should, at a minimum, meet WHO guidelines for drinking (potable) water quality.
- 4.32 If drinking (potable) water is insufficient to assure API quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical and chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established.

- 4.33 Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.
- 4.34 Where the manufacturer of a non-sterile API either intends or claims that it is suitable for use in further processing to produce a sterile FPP, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms and endotoxins.

4.4 Containment

- 4.40 Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.
- 4.41 Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g. certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.
- 4.42 Appropriate measures should be established and implemented to prevent cross-contamination, e.g. from personnel or materials, moving from one dedicated area to another.
- 4.43 Any production activities (including weighing, milling or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.

4.5 Lighting

- 4.50 Adequate lighting should be provided in all areas to facilitate cleaning, maintenance and proper operations.

4.6 Sewage and refuse

- 4.60 Sewage, refuse and other waste (e.g. solids, liquids, or gaseous byproducts from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

4.7 Sanitation and maintenance

- 4.70 Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

- 4.71 Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment and materials to be used in cleaning buildings and facilities.
- 4.72 When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging or labelling materials, intermediates and APIs.

5. Process equipment

5.1 Design and construction

- 5.10 Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate) and maintenance.
- 5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.
- 5.12 Production equipment should only be used within its qualified operating range.
- 5.13 Major equipment (e.g. reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.
- 5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food-grade lubricants and oils should be used.
- 5.15 Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.
- 5.16 A set of current drawings should be maintained for equipment and critical installations (e.g. instrumentation and utility systems).

5.2 Equipment maintenance and cleaning

- 5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventive maintenance of equipment.

- 5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:
- assignment of responsibility for cleaning of equipment;
 - cleaning schedules, including, where appropriate, sanitizing schedules;
 - a complete description of the methods and materials, including dilution of cleaning agents used to clean equipment;
 - when appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;
 - instructions for the removal or obliteration of previous batch identification;
 - instructions for the protection of clean equipment from contamination prior to use;
 - inspection of equipment for cleanliness immediately before use, if practical; and
 - establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.
- 5.22 Equipment and utensils should be cleaned, stored and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.
- 5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, this equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of microorganisms).
- 5.24 Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.
- 5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.
- 5.26 Equipment should be identified as to its contents and its cleanliness status by appropriate means.

5.3 Calibration

- 5.30 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

- 5.31 Equipment calibrations should be performed using standards traceable to certified standards, if these exist.
- 5.32 Records of these calibrations should be maintained.
- 5.33 The current calibration status of critical equipment should be known and verifiable.
- 5.34 Instruments that do not meet calibration criteria should not be used.
- 5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

5.4 Computerized systems

- 5.40 GMP-related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.
- 5.41 Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.
- 5.42 Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at the time of installation, a retrospective validation could be conducted if appropriate documentation is available.
- 5.43 Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g. the system being turned off and data not captured). There should be a record of any data change made, the previous entry, the person who made the change and when the change was made.
- 5.44 Written procedures should be available for the operation and maintenance of computerized systems.
- 5.45 Where critical data are being entered manually, there should be an additional check on the accuracy of the data entered. This can be done by a second operator or by the system itself.
- 5.46 Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

- 5.47 Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.
- 5.48 If system breakdowns or failures will result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.
- 5.49 Data can be recorded by a second means in addition to the computer system.

6. Documentation and records

6.1 Documentation system and specifications

- 6.10 All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.
- 6.11 The issuance, revision, superseding and withdrawal of all documents should be controlled with maintenance of revision histories.
- 6.12 A procedure should be established for retaining all appropriate documents (e.g. development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records and distribution records). The retention periods for these documents should be specified.
- 6.13 All production, control and distribution records should be retained for at least one year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least three years after the batch is completely distributed.
- 6.14 Entries in records should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed ensuring that the original entry remains readable.
- 6.15 During the retention period, originals or copies of records should be readily available at the establishment where the activities described in these records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.
- 6.16 Specifications, instructions, procedures and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other

accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

- 6.17 Specifications should be established and documented for raw materials, intermediates where necessary, APIs and labelling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.
- 6.18 If electronic signatures are used on documents they should be authenticated and secure.

6.2 Equipment cleaning and use record

- 6.20 Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should show the date, time (if appropriate), product and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.
- 6.21 If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance and use can be part of the batch record or maintained separately.

6.3 Records of raw materials, intermediates, API labelling and packaging materials

- 6.30 Records of raw materials, intermediates, API labelling and packaging materials should be maintained including:
- the name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for APIs; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt;
 - the results of any test or examination performed and the conclusions derived from this;
 - records tracing the use of materials;
 - documentation of the examination and review of API labelling and packaging material for conformity with established specifications; and

- the final decision regarding rejected raw materials, intermediates or API labelling and packaging materials.

6.31 Master (approved) labels should be maintained for comparison to issued labels.

6.4 Master production instructions (master production and control records)

6.40 To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated and signed by one person and independently checked, dated and signed by a person in the quality unit(s).

6.41 Master production instructions should include:

- the name of the intermediate or API being manufactured and an identifying document reference code, if applicable;
- a complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;
- an accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included where they are justified;
- the production location and major production equipment to be used;
- detailed production instructions, including the:
 - sequences to be followed,
 - ranges of process parameters to be used,
 - sampling instructions and in-process controls with their acceptance criteria, where appropriate,
 - time limits for completion of individual processing steps and/or the total process, where appropriate, and
 - expected yield ranges at appropriate phases of processing or time;
- where appropriate, special notations and precautions to be followed, or cross-references to these; and
- the instructions for storage of the intermediate or API to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

6.5 Batch production records (batch production and control records)

- 6.50 Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and is a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.
- 6.51 These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code, together with the date and time, can serve as the unique identifier until the final number is allocated.
- 6.52 Documentation of completion of each significant step in the batch production records (batch production and control records) should include:
- dates and, when appropriate, times;
 - identity of major equipment (e.g., reactors, driers and mills) used;
 - specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing;
 - actual results recorded for critical process parameters;
 - any sampling performed;
 - signatures of the persons performing and directly supervising or checking each critical step in the operation;
 - in-process and laboratory test results;
 - actual yield at appropriate phases or times;
 - description of packaging and label for intermediate or API;
 - representative label of API or intermediate if made commercially available;
 - any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately; and
 - results of release testing.
- 6.53 Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

6.6 Laboratory control records

6.60 Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- a description of samples received for testing, including the name of the material or its source, batch number or other distinctive code, the date the sample was taken and, where appropriate, the quantity and date the sample was received for testing;
- a statement of or reference to each test method used;
- a statement of the weight or measure of sample used for each test as described by the method;
- data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions;
- a complete record of all raw data generated during each test, in addition to graphs, charts and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested;
- a record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors and equivalency factors;
- a statement of the test results and how they compare with established acceptance criteria;
- the signature of the person who performed each test and the date(s) the tests were performed; and
- the date and signature of a second person showing that the original records have been reviewed for accuracy, completeness and compliance with established standards.

6.61 Complete records should also be maintained for:

- any modifications to an established analytical method;
- periodic calibration of laboratory instruments, apparatus, gauges and recording devices;
- all stability testing performed on APIs; and
- out-of-specification (OOS) investigations.

6.7 Batch production record review

6.70 Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and

labelling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

- 6.71 Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).
- 6.72 All deviation, investigation and OOS reports should be reviewed as part of the batch record review before the batch is released.
- 6.73 The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

7. Materials management

7.1 General controls

- 7.10 There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials.
- 7.11 Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.
- 7.12 Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s).
- 7.13 If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known to the intermediate and/or API manufacturer.
- 7.14 Changing the source of supply of critical raw materials should be done according to section 13, Change control.

7.2 Receipt and quarantine

- 7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labelling (including correlation between the name used by the supplier and the inhouse name, if these are different), damage to containers, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and then released for use.

- 7.21 Before incoming materials are mixed with existing stocks (e.g. solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.
- 7.22 If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:
- certificate of cleaning;
 - testing for trace impurities;
 - audit of the supplier.
- 7.23 Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.
- 7.24 Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

7.3 Sampling and testing of incoming production materials

- 7.30 At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below in section 7.32. A supplier's certificate of analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.
- 7.31 Supplier approval should include an evaluation that provides adequate evidence (e.g. past quality history) that the manufacturer can consistently provide material meeting specifications. Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the certificates of analysis. Reliability of certificates of analysis should be checked at regular intervals.
- 7.32 Processing aids, hazardous or highly toxic raw materials, other special materials or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's certificate of analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.

- 7.33 Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The decision on the number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, variability of the material, past quality history of the supplier and the quantity needed for analysis.
- 7.34 Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.
- 7.35 Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

7.4 Storage

- 7.40 Materials should be handled and stored in such a manner as to prevent degradation, contamination and cross-contamination.
- 7.41 Materials stored in fibre drums, bags or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.
- 7.42 Materials should be stored under conditions and for a period that will have no adverse affect on their quality and should normally be controlled so that the oldest stock is used first.
- 7.43 Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.
- 7.44 Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.

7.5 Re-evaluation

- 7.50 Materials should be re-evaluated as appropriate to determine their suitability for use (e.g. after prolonged storage or exposure to heat or humidity).

8. Production and in-process controls

8.1 Production operations

- 8.10 Raw materials for manufacturing of intermediates and APIs should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

8.11 If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

- material name and/or item code;
- receiving or control number;
- weight or measure of material in the new container; and
- re-evaluation or retest date if appropriate.

8.12 Critical weighing, measuring or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

8.13 Other critical activities should be witnessed or subjected to an equivalent control.

8.14 Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.

8.15 Any deviation should be documented and explained. Any critical deviation should be investigated.

8.16 The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems or alternative means.

8.17 Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

8.2 Time limits

8.20 If time limits are specified in the master production instruction (see section 6.41), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g. pH adjustment, hydrogenation or drying to a predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

8.21 Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

8.3 In-process sampling and controls

- 8.30 Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.
- 8.31 The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g. isolation and purification steps).
- 8.32 Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).
- 8.33 In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s)' approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.
- 8.34 Written procedures should describe the sampling methods for in-process materials, intermediates and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.
- 8.35 In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.
- 8.36 OOS investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

8.4 Blending batches of intermediates or APIs

- 8.40 For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g. collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

- 8.41 OOS batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.
- 8.42 Acceptable blending operations include but are not limited to:
- blending of small batches to increase batch size;
 - blending of tailings (i.e. relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch.
- 8.43 Blending processes should be adequately controlled and documented and the blended batch should be tested for conformance to established specifications where appropriate.
- 8.44 The batch record of the blending process should allow traceability back to the individual batches that make up the blend.
- 8.45 Where physical attributes of the API are critical (e.g. APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g. particle size distribution, bulk density and tap density) that may be affected by the blending process.
- 8.46 If the blending could adversely affect stability, stability testing of the final blended batches should be performed.
- 8.47 The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

8.5 Contamination control

- 8.50 Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carry-over should not result in the carryover of degradants or microbial contamination that may adversely alter the established impurity profile of the API.
- 8.51 Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.
- 8.52 Precautions to avoid contamination should be taken when APIs are handled after purification.

9. Packaging and identification labelling of APIs and intermediates

9.1 General

- 9.10 There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release and handling of packaging and labelling materials.
- 9.11 Packaging and labelling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.
- 9.12 Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing and whether they are accepted or rejected.

9.2 Packaging materials

- 9.20 Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.
- 9.21 Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive or absorptive to ensure that they do not alter the quality of the intermediate or API beyond the specified limits.
- 9.22 If containers are reused, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.

9.3 Label issuance and control

- 9.30 Access to the label storage areas should be limited to authorized personnel.
- 9.31 Procedures should be used to reconcile the quantities of labels issued, used and returned and to evaluate discrepancies found between the number of containers labelled and the number of labels issued. Such discrepancies should be investigated and the investigation should be approved by the quality unit(s).
- 9.32 All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be retained and stored in a manner that prevents mix-ups and provides proper identification.
- 9.33 Obsolete and outdated labels should be destroyed.

- 9.34 Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.
- 9.35 Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.
- 9.36 A printed label representative of those used should be included in the batch production record.

9.4 Packaging and labelling operations

- 9.40 There should be documented procedures designed to ensure that the correct packaging materials and labels are used.
- 9.41 Labelling operations should be designed to prevent mix-ups. They should be physically or spatially separated from operations involving other intermediates or APIs.
- 9.42 Labels used on containers of intermediates or APIs should indicate the name or identifying code, the batch number of the product and the storage conditions, when such information is critical to assure the quality of the intermediate or API.
- 9.43 If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents and special transport conditions and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, this date should be indicated on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or certificate of analysis.
- 9.44 Packaging and labelling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log or other documentation system.
- 9.45 Packaged and labelled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.
- 9.46 Intermediate or API containers that are transported outside the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

10. Storage and distribution

10.1 Warehousing procedures

- 10.10 Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.
- 10.11 Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.

10.2 Distribution procedures

- 10.20 APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.
- 10.21 APIs and intermediates should be transported in a manner that does not adversely affect their quality.
- 10.22 Special transport or storage conditions for an API or intermediate should be stated on the label.
- 10.23 The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.
- 10.24 A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

11. Laboratory controls

11.1 General controls

- 11.10 The independent quality unit(s) should have at its disposal adequate laboratory facilities.
- 11.11 There should be documented procedures describing sampling, testing, approval or rejection of materials and recording and storage of laboratory data. Laboratory records should be maintained in accordance with section 6.6.

- 11.12 All specifications, sampling plans and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).
- 11.13 Appropriate specifications should be established for APIs in accordance with accepted standards and be consistent with the manufacturing process. The specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.
- 11.14 Laboratory controls should be followed and documented at the time of performance. Any departures from the above-described procedures should be documented and explained.
- 11.15 Any OOS result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.
- 11.16 Reagents and standard solutions should be prepared and labelled following written procedures. “Use by” dates should be applied as appropriate for analytical reagents or standard solutions.
- 11.17 Primary reference standards should be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard’s storage and use in accordance with the supplier’s recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier’s recommendations.
- 11.18 Where a primary reference standard is not available from an officially recognized source, an “in-house primary standard” should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

- 11.19 Secondary reference standards should be appropriately prepared, identified, tested, approved and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

11.2 Testing of intermediates and APIs

- 11.20 For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.
- 11.21 An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed and classification of each identified impurity (e.g. inorganic, organic or solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs of herbal or animal tissue origin. Biotechnology considerations are covered in ICH Guideline Q6B (1).
- 11.22 The impurity profile should be compared at appropriate intervals with the impurity profile in the regulatory submission or compared with historical data in order to detect changes to the API resulting from modifications to raw materials, equipment operating parameters or the production process.
- 11.23 Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.

11.3 Validation of analytical procedures

See section 12.

11.4 Certificates of analysis

- 11.40 Authentic certificates of analysis should be issued for each batch of intermediate or API on request.
- 11.41 Information on the name of the intermediate or API, including where appropriate its grade, the batch number and the date of release, should be provided on the certificate of analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and certificate of analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or certificate of analysis.

- 11.42 The certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits and the numerical results obtained (if test results are numerical).
- 11.43 Certificates should be dated and signed by authorized personnel from the quality unit(s) and should show the name, address and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the certificate of analysis should show the name, address and telephone number of the repacker or reprocessor and a reference to the name of the original manufacturer.
- 11.44 If new certificates are issued by or on behalf of repackers or reprocessors, agents or brokers, these certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch certificate, a copy of which should be attached.

11.5 Stability monitoring of APIs

- 11.50 A documented, ongoing testing programme should be designed to monitor the stability characteristics of APIs and the results should be used to confirm appropriate storage conditions and retest or expiry dates.
- 11.51 The test procedures used in stability testing should be validated and be stability-indicating.
- 11.52 Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fibre drums, stability samples can be packaged in bags of the same material and in smaller drums of similar or identical material composition to the drums in which the API is marketed.
- 11.53 Normally the first three commercial production batches should be placed on the stability monitoring programme to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least two years, fewer than three batches can be used.
- 11.54 Thereafter at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring programme and tested at least annually to confirm the stability.
- 11.55 For APIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biological and other APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested

monthly for the first three months, and at three-monthly intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g. nine-month testing) can be considered.

- 11.56 Where appropriate, the stability storage conditions should be consistent with the WHO guidelines on stability.

11.6 Expiry and retest dating

- 11.60 When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g. published data and test results).
- 11.61 An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.
- 11.62 Preliminary API expiry or retest dates can be based on pilot-scale batches if:
- the pilot batches employ a method of manufacture and a procedure that simulates the final process to be used on a commercial manufacturing scale; and
 - the quality of the API represents the material to be made on a commercial scale.
- 11.63 A representative sample should be taken for the purpose of performing a retest.

11.7 Reserve/retention samples

- 11.70 The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing.
- 11.71 Appropriately identified reserve samples of each batch of API should be retained for one year after the expiry date assigned by the manufacturer to the batch, or for three years after distribution of the batch, whichever is the longer. For APIs with retest dates, similar reserve samples should be retained for three years after the batch has been completely distributed by the manufacturer.
- 11.72 The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

12. Validation

12.1 Validation policy

- 12.10 The company's overall policy, intentions and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems and personnel responsible for design, review, approval and documentation of each validation phase, should be documented.
- 12.11 The critical parameters and attributes should normally be identified during the development stage or from historical data and the ranges necessary for the reproducible operation should be defined. This should include:
- defining the API in terms of its critical product attributes;
 - identifying process parameters that could affect the critical quality attributes of the API;
 - determining the range for each critical process parameter expected to be used during routine manufacturing and process control.
- 12.12 Validation should extend to those operations determined to be critical to the quality and purity of the API.

12.2 Validation documentation

- 12.20 A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.
- 12.21 The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective or concurrent) and the number of process runs.
- 12.22 A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed and drawing the appropriate conclusions, including recommending changes to correct deficiencies.
- 12.23 Any variations from the validation protocol should be documented with appropriate justification.

12.3 Qualification

12.30 Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

- design qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose;
- installation qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements;
- operational qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges;
- performance qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

12.4 Approaches to process validation

12.40 Process validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

12.41 There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These three approaches and their applicability are outlined below.

12.42 Prospective validation should normally be performed for all API processes as defined in section 12.1.3. Prospective validation performed on an API process should be completed before the commercial distribution of the FPP manufactured from that API.

12.43 Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in FPPs for commercial distribution based on thorough monitoring and testing of the API batches.

- 12.44 An exception can be made for retrospective validation for well-established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities or the production process. This validation approach may be used where:
- (1) Critical quality attributes and critical process parameters have been identified.
 - (2) Appropriate in-process acceptance criteria and controls have been established.
 - (3) There have not been significant process or product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability.
 - (4) Impurity profiles have been established for the existing API.

- 12.45 Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

12.5 Process validation programme

- 12.50 The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g. complex API processes or API processes with prolonged completion times). Generally, for retrospective validation, data from 10 to 30 consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.

- 12.51 Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.
- 12.52 Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to or better than historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

12.6 Periodic review of validated systems

- 12.60 Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

12.7 Cleaning validation

- 12.70 Cleaning procedures should normally be validated. In general cleaning validation should be directed to those situations or process steps where contamination or carry-over of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.
- 12.71 Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity and stability.
- 12.72 The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labelled.
- 12.73 Sampling should include swabbing, rinsing or alternative methods (e.g. direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g. inner surfaces of hoses, transfer pipes, reactor tanks with small ports for handling toxic materials and small intricate equipment such as micronizers and microfluidizers).
- 12.74 Validated analytical methods with the sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable and verifiable and be based on the most deleterious residue. Limits can be established based on the

minimum known pharmacological, toxicological or physiological activity of the API or its most deleterious component.

- 12.75 Equipment cleaning or sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g. non-sterile APIs used to manufacture sterile products).
- 12.76 Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise remain undetected by sampling and/or analysis.

12.8 Validation of analytical methods

- 12.80 Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.
- 12.81 Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.
- 12.82 Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.
- 12.83 Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

13. Change control

- 13.10 A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.
- 13.11 Written procedures should cover the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical

methods, facilities, support systems, equipment (including computer hardware), processing steps, labelling and packaging materials and computer software.

- 13.12 Any proposals for relevant changes to GMP should be drafted, reviewed and approved by the appropriate organizational units and reviewed and approved by the quality unit(s).
- 13.13 The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on their nature and extent and the effects these changes may have on the process. Scientific judgement should be used to determine what additional testing and validation studies are appropriate to justify a change in a validated process.
- 13.14 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.
- 13.15 After the change has been implemented there should be an evaluation of the first batches produced or tested under the change.
- 13.16 The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability programme and/or can be added to the stability monitoring programme.
- 13.17 Manufacturers of the current dosage form should be notified of changes from established production and process control procedures that can impact the quality of the API.

14. Rejection and reuse of materials

14.1 Rejection

- 14.10 Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.

14.2 Reprocessing

- 14.20 Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation

steps (e.g. distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches it should be included as part of the standard manufacturing process.

- 14.21 Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.
- 14.22 Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely affected due to the potential formation of by-products and overreacted materials.

14.3 Reworking

- 14.30 Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for non-conformance should be performed.
- 14.31 Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.
- 14.32 Procedures should provide for comparing the impurity profile of each reworked batch with batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

14.4 Recovery of materials and solvents

- 14.40 Recovery (e.g. from mother liquor or filtrates) of reactants, intermediates or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.
- 14.41 Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored

to ensure that solvents meet appropriate standards before reuse or comingling with other approved materials.

- 14.42 Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.
- 14.43 The use of recovered solvents, mother liquors and other recovered materials should be adequately documented.

14.5 Returns

- 14.50 Returned intermediates or APIs should be identified as such and quarantined.
- 14.51 If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return, or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked or destroyed, as appropriate.
- 14.52 Records of returned intermediates or APIs should be maintained. For each return, documentation should include:
 - name and address of the consignee;
 - intermediate or API, batch number and quantity returned;
 - reason for return; and
 - use or disposal of the returned intermediate or API.

15. Complaints and recalls

- 15.10 All quality-related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.
- 15.11 Complaint records should include:
 - name and address of complainant;
 - name (and, where appropriate, title) and telephone number of person submitting the complaint;
 - nature of the complaint (including name and batch number of the API);
 - date the complaint was received;
 - action initially taken (including dates and identity of person taking the action);
 - any follow-up action taken;

- response provided to the originator of complaint (including date on which the response was sent); and
 - final decision on intermediate or API batch or lot.
- 15.12 Records of complaints should be retained in order to evaluate trends, product-related frequencies and severity with a view to taking additional, and if appropriate, immediate corrective action.
- 15.13 There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.
- 15.14 The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall and how the recalled material should be treated.
- 15.15 In the event of a serious or potentially life-threatening situation, local, national and/or international authorities should be informed and their advice sought.

16. Contract manufacturers (including laboratories)

- 16.10 All contract manufacturers (including laboratories) should comply with GMP defined in this guide. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.
- 16.11 Contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations taking place at the contract sites.
- 16.12 There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.
- 16.13 The contract should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.
- 16.14 Where subcontracting is allowed the contract acceptor should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements.
- 16.15 Manufacturing and laboratory records should be kept at the site where the activity takes place and be readily available.
- 16.16 Changes in the process, equipment, test methods, specifications or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

17. Agents, brokers, traders, distributors, repackers and relabellers

17.1 Applicability

- 17.10 This section applies to any party other than the original manufacturer who may trade and/or take possession of, repack, relabel, manipulate, distribute or store an API or intermediate.
- 17.11 All agents, brokers, traders, distributors, repackers and relabellers should comply with GMP as defined in this guide.

17.2 Traceability of distributed APIs and intermediates

- 17.20 Agents, brokers, traders, distributors, repackers or relabellers should maintain complete traceability of the APIs and intermediates that they distribute. Documents that should be retained and available should include:
- identity of original manufacturer;
 - address of original manufacturer;
 - purchase orders;
 - bills of lading (transportation documentation);
 - receipt documents;
 - name or designation of API or intermediate;
 - manufacturer's batch number;
 - transportation and distribution records;
 - all authentic certificates of analysis, including those of the original manufacturer; and
 - retest or expiry date.

17.3 Quality management

- 17.30 Agents, brokers, traders, distributors, repackers or relabellers should establish, document and implement an effective system of managing quality, as specified in section 2.

17.4 Repackaging, relabelling and holding of APIs and intermediates

- 17.40 Repackaging, relabelling and holding of APIs and intermediates should be performed under appropriate GMP controls as stipulated in this guide, to avoid mix-ups and loss of API or intermediate identity or purity.

- 17.41 Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

17.5 Stability

- 17.50 Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the manufacturer of the API or intermediate.

17.6 Transfer of information

- 17.60 Agents, brokers, distributors, repackers or relabellers should transfer all quality or regulatory information received from the manufacturer of an API or intermediate to the customer, and from the customer to the manufacturer of the API or intermediate.
- 17.61 The agent, broker, trader, distributor, repacker or relabeller who supplies the API or intermediate to the customer should provide the name of the original manufacturer of the API or intermediate and the batch number(s) supplied.
- 17.62 The agent should also provide the identity of the manufacturer of the original API or intermediate to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between the authorized agents and the original manufacturer of the API or intermediate. (In this context “authorized” refers to authorized by the manufacturer.)
- 17.63 The specific guidance for certificates of analysis included in section 11.4 should be met.

17.7 Handling of complaints and recalls

- 17.70 Agents, brokers, traders, distributors, repackers or relabellers should maintain records of complaints and recalls as specified in section 15 for all complaints and recalls that come to their attention.
- 17.71 If the situation warrants, the agents, brokers, traders, distributors, repackers or relabellers should review the complaint with the manufacturer of the original API or intermediate to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.

- 17.72 Where a complaint is referred to the original manufacturer of the API or intermediate, the record maintained by the agents, brokers, traders, distributors, repackers or relabellers should include any response received from the original manufacturer of the API or intermediate (including date and information provided).

17.8 Handling of returns

- 17.80 Returns should be handled as specified in section 14.5.3. The agents, brokers, traders, distributors, repackers or relabellers should maintain documentation of returned APIs and intermediates.

18. Specific guidance for APIs manufactured by cell culture/fermentation²

18.1 General

- 18.10 Section 18 is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for “classical” processes for production of small molecules and for processes using recombinant and non-recombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.
- 18.11 The term “biotechnological process” (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this Section. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.

² This section has been referred to the Expert Committee on Biological Standardization for discussion and consideration. Reproduced here but currently not adopted by the aforementioned Expert Committee.

- 18.12 The term “classical fermentation” refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g. irradiation or chemical mutagenesis) to produce APIs. APIs produced by “classical fermentation” are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.
- 18.13 Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.
- 18.14 Appropriate controls should be established at all stages of manufacturing to assure intermediate and/or API quality. While this guide starts at the cell culture/fermentation step, prior steps (e.g. cell banking) should be performed under appropriate process controls. This guide covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.
- 18.15 Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for quality of the environment and the frequency of monitoring should depend on the step in production and the production conditions (open, closed or contained systems).
- 18.16 In general, process controls should take into account:
- maintenance of the working cell bank (where appropriate);
 - proper inoculation and expansion of the culture;
 - control of the critical operating parameters during fermentation/cell culture;
 - monitoring of the process for cell growth, viability (for most cell culture processes) and productivity where appropriate;
 - harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality;
 - monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production; and
 - viral safety concerns as described in ICH Guideline Q5A (2).

18.17 Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

18.2 Cell bank maintenance and record keeping

18.20 Access to cell banks should be limited to authorized personnel.

18.21 Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.

18.22 Records of the use of the vials from the cell banks and storage conditions should be maintained.

18.23 Where appropriate, cell banks should be periodically monitored to determine suitability for use.

18.24 See ICH Guideline Q5D (3) for a more complete discussion of cell banking.

18.3 Cell culture/fermentation

18.30 Where aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.

18.31 Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.

18.32 Personnel should be appropriately gowned and take special precautions handling the cultures.

18.33 Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.

18.34 Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, and sanitized or sterilized.

18.35 Culture media should be sterilized before use when appropriate to protect the quality of the API.

- 18.36 There should be appropriate procedures in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.
- 18.37 Records of contamination events should be maintained.
- 18.38 Shared (multiproduct) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

18.4 Harvesting, isolation and purification

- 18.40 Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, should be performed in equipment and areas designed to minimize the risk of contamination.
- 18.41 Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.
- 18.42 All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.
- 18.43 If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.
- 18.44 Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

18.5 Viral removal/inactivation steps

- 18.50 See the ICH Guideline Q5A (2) for more specific information.
- 18.51 Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.
- 18.52 Appropriate precautions should be taken to prevent potential viral contamination from pre-viral to post-viral removal/inactivation steps. Therefore, open processing

should be performed in areas that are separate from other processing activities and have separate air handling units.

- 18.53 The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carry-over (e.g. through equipment or environment) from previous steps.

19. APIs for use in clinical trials

19.1 General

- 19.10 Not all the controls in the previous sections of this guide are appropriate for the manufacture of a new API for investigational use during its development. Section 19 provides specific guidance unique to these circumstances.

- 19.11 The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the pharmaceutical product incorporating the API. Process and test procedures should be flexible to allow for changes to be made as knowledge of the process increases and clinical testing of a pharmaceutical product progresses from the preclinical stages through the clinical stages. Once pharmaceutical development reaches the stage where the API is produced for use in pharmaceutical products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

19.2 Quality

- 19.20 Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism for the approval of each batch.
- 19.21 A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.
- 19.22 Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.
- 19.23 Quality measures should include a system for testing of raw materials, packaging materials, intermediates and APIs.
- 19.24 Process and quality problems should be evaluated.
- 19.25 Labelling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

19.3 Equipment and facilities

- 19.30 During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use.
- 19.31 Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

19.4 Control of raw materials

- 19.40 Raw materials used in production of APIs for use in clinical trials should be evaluated by testing or be received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous a supplier's analysis should suffice.
- 19.41 In some instances the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e. use testing) rather than on analytical testing alone.

19.5 Production

- 19.50 The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records or by other appropriate means. These documents should include information on the use of production materials, equipment, processing and scientific observations.
- 19.51 Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

19.6 Validation

- 19.60 Process validation for the production of APIs for use in clinical trials is normally inappropriate where a single API batch is produced or where process changes during development of an API make batch replication difficult or inexact. The combination of controls, calibration and, where appropriate, equipment qualification assures quality of the API during this development phase.
- 19.61 Process validation should be conducted in accordance with section 12 when batches are produced for commercial use, even when such batches are produced on a pilot scale or small scale.

19.7 Changes

- 19.70 Changes are expected during development as knowledge is gained and the production is scaled up. Every change in the production, specifications or test procedures should be adequately recorded.

19.8 Laboratory controls

- 19.80 While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated they should be scientifically sound.
- 19.81 A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination or discontinuation of an application.
- 19.82 Expiry and retest dating as defined in section 11.6 applies to existing APIs used in clinical trials. For new APIs section 11.6 does not normally apply in early stages of clinical trials.

19.9 Documentation

- 19.90 A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.
- 19.91 The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.
- 19.92 A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination or discontinuation of an application.

20. Glossary

acceptance criteria

Numerical limits, ranges or other suitable measures for acceptance of test results.

active pharmaceutical ingredient (API) (or pharmaceutical substance)

Any substance or mixture of substances intended to be used in the manufacture of a finished pharmaceutical product (FPP) and that, when used in the production of a pharmaceutical product, becomes an active ingredient of the pharmaceutical product.

Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

API starting material

A raw material, intermediate or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement or produced in-house. API starting materials normally have defined chemical properties and structure.

batch (or lot)

A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

batch number (or lot number)

A unique combination of numbers, letters and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

bioburden

The level and type (e.g. objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

calibration

The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

computer system

A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions.

computerized system

A process or operation integrated with a computer system.

contamination

The undesired introduction of impurities of a chemical or microbiological nature or of foreign matter into or on to a raw material, intermediate or API during production, sampling, packaging or repackaging, storage or transport.

contract manufacturer

A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

critical

Describes a process step, process condition, test requirement or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

cross-contamination

Contamination of a material or product with another material or product.

deviation

Departure from an approved instruction or established standard.

expiry date (or expiration date)

The date placed on the container or labels of an API designating the time during which the API is expected to remain within established shelf-life specifications if stored under defined conditions and after which it should not be used.

finished pharmaceutical product (FPP)

ICH: The dosage form in the final immediate packaging intended for marketing (reference Q1A (4)).

WHO: A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more APIs.

impurity

Any component present in the intermediate or API that is not the desired entity.

impurity profile

A description of the identified and unidentified impurities present in an API.

in-process control (or process control)

Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

intermediate

A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated.

(Note: this guide only addresses those intermediates produced after the point that the company has defined as the point at which the production of the API begins.)

lot

See Batch.

lot number

See Batch number.

manufacture

All operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage and distribution of APIs and related controls.

material

A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs and packaging and labelling materials.

mother liquor

The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API and/or impurities. It may be used for further processing.

packaging material

Any material intended to protect an intermediate or API during storage and transport.

pharmaceutical substance

See Active pharmaceutical ingredient.

procedure

A documented description of the operations to be performed, the precautions to be taken and measures to be applied, directly or indirectly related to the manufacture of an intermediate or API.

process aids

Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid or activated carbon).

process control

See In-process control.

production

All operations involved in the preparation of an API from receipt of materials through processing and packaging of the API.

qualification

Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

quality assurance (QA)

The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

quality control (QC)

Checking or testing that specifications are met.

quality unit(s)

An organizational unit independent of production which fulfils both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

quarantine

The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

raw material

A general term used to denote starting materials, reagents and solvents intended for use in the production of intermediates or APIs.

reference standard, primary

A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be:

- obtained from an officially recognized source;
- prepared by independent synthesis;
- obtained from existing production material of high purity; or
- prepared by further purification of existing production material.

reference standard, secondary

A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

reprocessing

Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other

appropriate chemical or physical manipulation steps (e.g. distillation, filtration, chromatography or milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process and not to be reprocessing.

retest date

The date when a material should be re-examined to ensure that it is still suitable for use.

reworking

Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g. recrystallizing with a different solvent).

signature (signed)

See Signed.

signed (signature)

The record of the individual who performed a particular action or review. This record can be in the form of initials, full handwritten signature, personal seal or an authenticated and secure electronic signature.

solvent

An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

specification

A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. “Conformance to specification” means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

validation

A documented programme that provides a high degree of assurance that a specific process, method or system will consistently produce a result meeting predetermined acceptance criteria.

validation protocol

A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters and operating ranges, product characteristics, sampling, test data to be collected, number of validation runs and acceptable test results.

yield, expected

The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot-scale or manufacturing data.

yield, theoretical

The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

References

1. *ICH Harmonised Tripartite Guideline: Specifications: test procedures and acceptance criteria for biotechnological/biological products Q6B*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1999.
2. *ICH Harmonised Tripartite Guideline: Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin Q5A*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1999.
3. *ICH Harmonised Tripartite Guideline: Derivation and characterisation of cell substrates used for production of biotechnological/biological products Q5D*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1997.
4. *ICH Harmonised Tripartite Guideline: Stability testing of new drug substances and products Q1A*. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2003.

Appendix 1

List of references for related WHO guidelines

Distribution

Good trade and distribution practices for pharmaceutical starting materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2003, Annex 2 (WHO Technical Report Series, No. 917).

WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2003, Annex 3 (WHO Technical Report Series, No. 917).

Guide to good storage practices for pharmaceuticals In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003, Annex 9 (WHO Technical Report Series, No. 908).

Production

Good Manufacturing Practices for Pharmaceutical Products: Main Principles. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report*. Geneva, World Health Organization, 2003, Annex 4 (WHO Technical Report Series, No. 908).

Good manufacturing practices: requirement for the sampling of starting materials (amendment). In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005, Annex 2 (WHO Technical Report Series, No. 929).

Sterile pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002, Annex 6 (WHO Technical Report Series, No. 902).

Investigational pharmaceutical products for clinical trials in humans. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 7 (WHO Technical Report Series, No. 863).

Herbal medicinal products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006, Annex 3 (WHO Technical Report Series, No. 937).

Water for pharmaceutical use. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005, Annex 3 (WHO Technical Report Series, No. 929).

Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006, Annex 2 (WHO Technical Report Series, No. 937).

Validation. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization, 2006, Annex 4 (WHO Technical Report Series, No. 937).

Quality control

The International Pharmacopoeia (Ph. Int.) — Fourth Edition + First Supplement. Geneva, World Health Organization, 2006.

General guidelines for the establishment, maintenance and distribution of chemical reference substances. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007, Annex 3 (WHO Technical Report Series, No. 943).

Considerations for requesting analyses of drug samples. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002, Annex 4 (WHO Technical Report Series, No. 902).

Model certificate of analysis. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002, Annex 10 (WHO Technical Report Series, No. 902).

Related regulatory standards

Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009, Annex 2 (WHO Technical Report Series, No. 953).

Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report*. Geneva, World Health Organization, 2009, Annex 4 (WHO Technical Report Series, No. 953).

Guidelines on active pharmaceutical ingredient master file procedure. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-second report*. Geneva, World Health Organization, 2008, Annex 4 (WHO Technical Report Series, No. 948).

Guidance on variations to a prequalified product dossier. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first report*. Geneva, World Health Organization, 2007, Annex 6 (WHO Technical Report Series, No. 943).

WHO guidelines for sampling of pharmaceutical products and related materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report.* Geneva, World Health Organization, 2005, Annex 4 (WHO Technical Report Series, No. 929).

Appendix 2

General notes: additional clarifications and explanations

- 2.1.1 The intent of this clause is that senior management of the API manufacturer has the responsibility to ensure that there is an effective quality management system in place and that all employees are made aware of their roles and responsibilities in assuring the quality of the API(s) produced.
- 2.3 The intent of this clause is to specify the roles and responsibilities that should apply to production activities and, in particular, that these responsibilities should not be delegated to non-production personnel within the company or to any persons outside the company.
- 5.2.1 This clause requires a written standard operating procedure (SOP) covering the maintenance of equipment. Important information to specify in this SOP should include:
- who is responsible for coordinating equipment maintenance activities (usually production management or engineering management);
 - a provision that a schedule of planned preventive maintenance of equipment should be available (a useful reference is *ISPE Good Practice Guide: Maintenance. May 2009*) (1);
 - a statement of the necessity to follow proper change control procedures where non-routine repairs, or modifications, replacements or other activities, are required.
- 7.1.2 There is an expectation that suppliers of critical materials should be subject to on-site audits as part of the company's supplier qualification programme.
- 7.2.1 There is an expectation that upon receipt and before acceptance of materials, each container or grouping of containers of materials should be examined visually for correct labelling, including correlation between the name used by the supplier and the in-house name. If these names are different, both names should be recorded and verified against a previously approved list of synonyms and checked by a scientifically qualified person.
- 7.3.1 This clause requires that at least one test be performed to verify the identity of each batch of material received. For clarification, one test for identity may not be sufficient in the majority of cases as this is dependent on various aspects, including supplier qualification.

- 11.7.3 For clarification, the reserve sample should be stored in a packaging system designed to give maximum protection of the API against change over time, e.g. a glass bottle with tightly fitted cap.
17. Refer to WHO GTDP (2) and WHO GMP for excipients (3).
18. See footnote on p. 174.

API starting material

As discussed in this document the introduction of the API starting material into the manufacturing process is where the requirements of GMP commence.

The API starting material itself needs to be proposed and justified by the manufacturer and accepted as such by assessors. This justification should be documented and be available for review by WHO GMP inspectors.

The API starting material should be fully characterized according to identity and purity. In addition, the steps prior to the step where the API starting material appears, which may involve “starting materials for synthesis”, should be available in the form of a flow chart.

In general, the starting materials for synthesis should:

- be a synthetic precursor one or more synthetic steps prior to the final API intermediate;
- be a well characterized, isolated and purified substance with a fully elucidated structure;
- have well defined specifications which include one or more specific identity tests, and tests and limits for potency, specified and unspecified impurities and total impurities.

References

1. International Society for Pharmaceutical Engineering. *ISPE good practice guide: maintenance*. 2009 (http://www.ispe.org/cs/ispe_good_practice_guides_section/ispe_good_practice_guides).
2. Good trade and distribution practices for pharmaceutical starting materials. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report*. Geneva, World Health Organization, 2003, Annex 2 (WHO Technical Report Series, No. 917) (https://iris.who.int/bitstream/handle/10665/42851/WHO_TRS_917.pdf?sequence=1&isAllowed=y).
3. WHO GMP for excipients In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fifth report*. Geneva, World Health Organization, 1999, Annex 5 (WHO Technical Report Series, No. 885) (https://iris.who.int/bitstream/handle/10665/42145/WHO_TRS_885.pdf?sequence=1&isAllowed=y); and in: *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2*, 2nd updated ed., *Good manufacturing practices and inspection*. Geneva, World Health Organization, 2007.

2.2 Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients

Annex 5, WHO Technical Report Series, 885,
1999 (under revision)

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1. General considerations

These guidelines, which focus on aspects of good manufacturing practices (GMP) specific for pharmaceutical excipients, supplement the general GMP guidelines for pharmaceutical products published by WHO.¹ They also incorporate some of the concepts for quality management systems determined by the International Organization for Standardization (ISO).

Excipients significantly affect the finished product quality, in some cases making up almost the entire formulation. Many pharmaceutical excipients are used in much greater quantities in other industries, such as the food, cosmetic or industrial chemical industry. Consistency and rigour of product specifications may not be as critical in these industries as they are for pharmaceuticals, and many of the excipients used are highly variable. Therefore, a programme must be in place which will monitor these excipients and provide the necessary assurance that they meet the quality parameters for pharmaceutical manufacturing processes. The purpose of this document is to lay out some criteria which may be used to achieve this level of assurance.

The formulator of the finished dosage form is highly dependent on the excipient manufacturer to provide bulk substances that are uniform in chemical and physical characteristics. This is particularly important in the product approval process, where bioequivalence comparisons are made between clinical bioequivalence ("biobatch") production and commercial scale-up batches. To provide adequate assurance of drug product performance *in vivo*, the excipient used to manufacture commercial batches should not differ significantly from that used in biobatches. Where significant differences may be expected, additional testing by the finished dosage manufacturer may be required to establish the bioequivalence of the finished product. It remains equally important to ensure that the bioequivalence of subsequent, postapproval commercial batches of drug products is not adversely affected over time.

In general, excipients are used as purchased, with no further refinement or purification. Consequently, impurities present in the excipient will be carried over to the finished dosage form. While dosage form manufacturers may have a limited control over excipient quality (i.e. by obtaining certificates of analysis and testing representative samples), the excipient manufacturer has greater control over physical characteristics, quality, and the presence of trace-level impurities in the excipient. The excipient manufacturer should perform periodic performance trend analyses of processes, and the purchaser of the material should also maintain a trend analysis of all testing done on the excipient upon receipt.

¹ Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).

In the manufacture of excipients, the environmental conditions, equipment and operational techniques employed reflect the chemical industry rather than the finished drug manufacturing industry. In some processes chemical and biochemical mechanisms have not been fully characterized; therefore, the methods and procedures for materials accountability will often differ from those applicable to the manufacture of finished dosage forms. Many chemical processes are performed in closed systems that tend to provide protection against contamination, even when the reaction vessels are not enclosed in buildings. However, this does not preclude the introduction of contaminants from equipment, materials used to protect equipment, corrosion, cleaning and personnel.

Some excipient manufacturing processes may require observance of GMP applicable to finished drug products or bulk active ingredients because of the excipient's intended use. However, such observance is neither feasible nor necessary in many processes, particularly during the early processing steps. The requirements increase as the process progresses. At some logical processing step, usually well before the final finishing operation, appropriate GMP should be imposed and maintained throughout the remainder of the process. To determine the processing step at which these GMP should be implemented, good judgement and a thorough knowledge of the process are required. A detailed process flow should identify the unit operations, equipment used, stages at which various substances are added, key steps in the process, critical parameters (time, temperature, pressure, etc.) and monitoring points.

An excipient manufacturer should be able to identify critical or key points in the process where selective intermediate sampling and testing is necessary in order to monitor process performance. Towards the end of the process, the records should be increasingly thorough.

Significant processing steps, required to produce an excipient that meets the established physical and chemical criteria, should be identified by the excipient manufacturer. These steps can involve a number of unit operations or unit processes. Unit operations include physical processing steps involving energy transfer where there is no chemical change of the molecule. Unit processes are those processing steps where the molecule undergoes a chemical change.

Significant processing steps include but are not limited to the following:

- Phase changes involving either the desired molecule, a solvent, inert carrier or vehicle (e.g. dissolution, crystallization, evaporation, drying, sublimation, distillation or absorption).
- Phase separation (e.g. filtration or centrifugation).
- Chemical changes involving the desired molecule (e.g. removal or addition of water of hydration, acetylation, formation of a salt).
- Adjustments of the solution containing the molecule (e.g. adjustment of pH).

- Precision measurement of added excipient components, in-process solutions, recycled materials (e.g. weighing, volumetric measuring).
- Mixing of multiple components.
- Changes that occur in surface area, particle size or batch uniformity (e.g. milling, agglomeration, blending).

Automated process controls and processing equipment are more likely to be used in an excipient plant than in a plant manufacturing finished dosage forms. Use of automated equipment is appropriate when adequate inspection, calibration, and maintenance procedures are performed. Production equipment and operations will vary depending on the type of excipient being produced, the scale of production, and the type of operation (i.e. batch versus continuous).

ISO “certification” for excipient manufacture is increasingly being required by final dosage formulators in the USA, Europe and Japan. Compliance to the International Standards of ISO 9000 series, in particular to ISO 9002, can confer greater acceptability of a supplier’s excipients in world markets. There is additional value to applying the principles of ISO 9000 to excipient manufacture, since quality system measures enhance GMP. Such ISO considerations as conformance to specific customer requirements, purchase of raw materials and statistical techniques benefit both the excipient customer and the manufacturer, and strengthen the relationship between the two.

It is therefore recommended that excipient manufacturers establish and implement a formal company-wide quality policy. Management should be committed to this policy and should appoint appropriate company personnel to be responsible for coordination and implementation of the quality system. Management should participate in the development of the company’s quality policy and provide the resources necessary for development, maintenance and periodic review of such a policy and quality system. Any significant changes in the processes should be validated with respect to excipient performance. It is recommended that all pharmaceutical manufacturers and also local agents should be informed of these changes. Ideally, excipient manufacturers should not subcontract any part of their process without the explicit knowledge of the pharmaceutical manufacturer.

Safe handling instructions should be provided by the excipient manufacturer to ensure that the purchaser is adequately equipped to handle the material. This should include information on the material’s toxicity and the measures to be taken upon accidental exposure. The equipment requirements for proper handling of the material should also be established.

2. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

commingling

The blending of carry-over material from one grade of an excipient with another, usually due to a continuous process.

*drug master file*²

Detailed information concerning a specific facility, process or product submitted to the drug regulatory authority, intended for incorporation into the application for marketing authorization.

model product

A product which simulates a group of similar products.

mother liquor

A concentrated solution from which the product is obtained by evaporation, freezing, and/or crystallization.

pharmaceutical excipients

Substances, other than the active ingredient, which have been appropriately evaluated for safety and are included in a drug delivery system to:

- aid in the processing of the drug delivery system during its manufacture;
- protect, support or enhance stability, bioavailability, or patient acceptability;
- assist in product identification; or
- enhance any other attribute of the overall safety and effectiveness of the drug during storage or use.

3. Self-inspection and quality audits

An inspection team consisting of appropriate personnel (e.g. auditors, engineers, laboratory analysts, purchasing agents, computer experts) should participate in inspections. The operational limitations and validation of the critical processing steps of a production process should be examined, to make sure that the manufacturer is taking adequate steps to check that the process works consistently.

The excipient's end use should be identified and considered during inspection of excipient manufacturers. It is particularly important to know whether the excipient

² This term appears to be specific to United States regulations.

is a direct or indirect component of a drug dosage form; whether the excipient will be used in the preparation of a sterile dosage form; and whether the excipient is presented as pyrogen/endotoxin free. The excipient manufacturer is responsible for ensuring that excipients are pyrogen free if the manufacturer makes such a representation in specifications, labels or a drug master file.

A good starting point for an excipient plant inspection is a review of the following areas:

- Non-conformance, such as the rejection of a batch not complying with specifications, return of a product by a customer, or recall of a product. The cause of non-conformance should have been determined by the manufacturer, a report of the investigation prepared, and subsequent corrective action initiated and documented. Records and documents should be reviewed to ensure that such non-conformance is not the result of a poorly developed or inconsistent process.
- Complaint files. Customers may report some aspects of product attributes that are not entirely suitable for their use. These may be caused by impurities or inconsistencies in the excipient manufacturing process.
- Change control documentation.
- Master formula and batch production records. Frequent revisions may reveal problems in the production process.
- Specifications for the presence of unreacted intermediates and solvent residues in the finished excipient.
- Storage areas for rejected products.

In evaluating the adequacy of measures taken to preclude contamination of materials in the process, it is appropriate to consider the following factors:

- Type of system (e.g. open or closed). “Closed” systems in chemical plants are often not closed when they are being charged and/or when the final product is being removed. Also, the same reaction vessels are sometimes used for different reactions.
- Form of the material (e.g. wet or dry).
- Stage of processing and use of the equipment and/or area (e.g. multipurpose or dedicated).

Other factors that should be considered in evaluating an excipient plant are:

- Degree of exposure of the material to adverse environmental conditions.
- Relative ease and thoroughness of clean-up.
- Sterile versus non-sterile operations.

4. Equipment

4.1 Use of equipment

Many excipients are produced using multipurpose equipment. Fermentation tanks, reactors, driers, grinders, centrifuges and other pieces of equipment are readily used or adapted for a variety of products. With few exceptions such multiple usage is satisfactory provided the equipment can be adequately cleaned according to written procedures. Equipment that contains tarry or gummy residues that cannot be removed easily should be dedicated for use with these products only.

Some fermentation tanks, reaction vessels, and other equipment are not situated within a building and a considerable amount of processing occurs out of doors. Such processing is acceptable provided it occurs in a closed system.

Where temperature control is important, temperature recording devices should be used, with recording charts kept as part of the batch record.

4.2 Cleaning programme

Where multipurpose equipment is in use, it is important to be able to determine previous usage when investigating cross-contamination or the possibility of such contamination. An equipment cleaning and use log, while desirable and perhaps preferable, is not the only method of determining prior use. Any documentation system which clearly identifies the previous batch and shows that the equipment was cleaned is acceptable. For operations where multiple grades of the same chemical entity are processed, there must be documentation showing that the previous grade was removed. Validation data must exist to prove acceptability of the cleaning procedure.

Cleaning of multiple-use equipment should be confirmed. The manufacturer should determine the effectiveness of the cleaning procedure for each excipient or intermediate chemical used in that particular piece of equipment. The validation data required depend on the types of materials being made in the multiple-use equipment and the impact of trace contaminants on drug safety and performance. Validation data should verify that the cleaning process has removed residues to an acceptable level.

As an example, an equipment cleaning programme may include, but is not limited to, the following:

4.2.1 Detailed cleaning procedure

There should be a written equipment cleaning procedure that provides details of what should be done and which cleaning materials should be used. Some manufacturers list the specific solvents used for each excipient and intermediate.

4.2.2 Sampling plan

There should be some periodic testing after cleaning, to ensure that the surface has been cleaned to the required level. One common method is to analyse the final rinse water or solvent for the presence of the substance last used in that piece of equipment. In some cases, visual inspections may be appropriate. A specific analytical method to determinate residual substances may not always be available, but is preferred. The need for an analytical method would be based on the potential adverse effect on product quality, performance or safety.

When safety is a concern, there should be a specific analytical determination for a residual substance.

4.2.3 Analytical methods/cleaning limits

The toxicity of the residual materials should be considered when deciding on the appropriate analytical method and the residual cleaning limits. The residue limits established for each piece of apparatus should be practical, achievable and verifiable. The manufacturer should be able to show, with supporting data, that the residual level permitted is scientifically based. Another factor to consider is the possible non-uniformity of the residue. The level of residue found by random sampling, such as taking a swab from a limited area on a piece of equipment, does not necessarily represent the highest level of contamination.

5. Materials

5.1 General

In the case of labile products that may be sensitive to environmental factors such as air, light, water, heat or cold, appropriate manufacturing and storage conditions must be used to ensure product quality throughout the process.

5.2 Starting materials

The excipient manufacturer should verify that the supplier of starting materials and components can meet the agreed-upon requirements. This may require periodic audits of the vendor's plant if necessary. Purchasing agreements should contain data clearly describing the product ordered including, where applicable, the following:

- The name, type, class, style, grade, item code numbers or other precise identification as appropriate.
- Drawings, process requirements, inspection instructions and other relevant technical data, including requirements for approval or verification of product, procedures, process equipment and personnel.

Starting materials, including solvents and recovered solvents, are sometimes stored in silos or other large containers, making precise separation of batches difficult. Usage of such materials should be demonstrated, via inventory or other records, with reasonable accuracy.

When purchased and recovered solvents are commingled, the suitability of the recovered solvent must be demonstrated through either validation or actual testing. The purchased materials should comply with existing specifications.

Outdoor storage of starting materials (e.g. acids, other corrosive substances, explosive materials) is acceptable if the containers give suitable protection to their contents, identifying labels remain legible and containers are adequately cleaned prior to opening and use.

5.3 Rejected and recovered materials

Any starting material, intermediate or finished excipient not complying with specifications must be clearly identified and segregated to prevent inadvertent use or release for sale. A record of noncompliance should be maintained. All cases of non-compliance should be investigated to identify the root cause.

These materials may be:

- reprocessed/reworked to meet the specified requirements;
- regraded for alternative applications; or
- rejected or scrapped.

Occasional reprocessing/reworking of an excipient may be acceptable. However, relying on the final testing only of the reprocessed excipient to demonstrate compliance to specification is not acceptable. The quality of the reprocessed material must be evaluated and documented showing adequate investigation and demonstrating that the reprocessed excipient is at least equivalent to other acceptable excipients. When reprocessing has to be done frequently, it may be an indication that the process, work instruction or training is inadequate and needs to be adjusted or reinforced.

5.4 Returned excipients

Returned excipients should be identified as such and kept. If the conditions under which the products have been stored and shipped or if the condition of the container itself casts doubt on the safety, quality or purity of the excipient, the product should be destroyed, unless thorough examination, testing, or other investigation shows that the product meets the appropriate predefined standards. If returned excipient containers are reused, all previous labelling should be removed or defaced. If the containers are used repeatedly solely for the same excipient, all previous batch numbers, or the entire label, should be removed or completely obliterated.

5.5 Storage practices

Pharmaceutical excipients should be stored under conditions established by the manufacturer on the basis of stability data. Records should be kept of the distribution of each batch of pharmaceutical excipient, to facilitate the recall of the batch if necessary, according to written procedures

6. Documentation

6.1 General

The excipient manufacturer should have a system to cover all documents and data that relate to the requirements of the quality system. Documents, and subsequent changes to the documents, should be reviewed and approved by designated personnel before being issued to the appropriate areas identified in the documents. A record should be kept of where the documents are located.

The following minimal requirements for documentation should be applied:

- To assign a unique batch number to the excipient to be released and/or certified.
- To prepare a batch record.
- To demonstrate that the batch has been prepared under GMP conditions from the processing point at which excipient GMP have been applied.
- To demonstrate that the batch is homogeneous within the manufacturer's specifications. This does not require a final blending of continuous process material, if process controls can demonstrate compliance with specifications throughout the batch.
- To demonstrate that the batch has not been commingled with material from other batches for the purpose of either hiding or diluting an adulterated substance.
- To demonstrate that the batch has been sampled in accordance with a sampling plan that ensures a representative sample of the batch is taken.
- To demonstrate that the batch has been analysed using scientifically established tests and methods designed to ensure that the product meets accepted standards and specifications for quality, identity and purity.
- To demonstrate that the batch has stability data to support the intended period of use; these data can be obtained from actual studies on the specific excipient or from applicable "model product" stability studies that can reasonably be expected to simulate the performance of the excipient.

6.2 Specifications

Starting material specifications should be organized to separate those tests that are routine from those that are performed infrequently or only for new suppliers. Relevant pharmacopoeial monographs, when available, provide a basis for the development of internal manufacturer's specifications.

A positive identification test uniquely applicable to the excipients should be established through analytical technology, such as infrared spectrophotometry and chromatography.

It is important that manufacturers identify and set appropriate limits for impurities. These limits should be based upon appropriate toxicological data, or limits described in national compendial requirements. Manufacturing processes should be adequately controlled so that the impurities do not exceed such established specifications.

Many excipients are extracted from or purified by the use of organic solvents. These solvents are normally removed by drying the moist excipient. In view of the varying and sometimes unknown toxicity of solvents, it is important that excipient specifications include tests and limits for residues of solvents and other reactants.

Container specifications should be established for all excipients to assure consistency in protecting the product during transport from the excipient manufacturer to the pharmaceutical producer. The specifications should not only provide for containers that maintain the stability of the product, but should also meet requirements for protection during shipping, against insect infestation, during handling, etc.

6.3 Batch production records

Computer systems are increasingly used to initiate, monitor, adjust and otherwise control manufacturing processes. These operations may be accompanied by recording charts that show key parameters (e.g. temperature) at suitable intervals, or even continuously, throughout the process. In other cases, key measurements (e.g. pH) may be displayed temporarily on a monitor screen, but are not available in hard copy.

Records showing addition of ingredients, actual performance of operations by identifiable individuals, and other information usually seen in conventional records, may be missing. When computers and other sophisticated equipment are employed, the emphasis must change from conventional, hand-written records to:

- systems and procedures that show the equipment and software is in fact performing as intended;
- checking and calibration of the equipment at appropriate intervals;
- retention of suitable back-up systems such as copies of the program and files, duplicate tapes or microfilm;
- assurance that changes in the program are made only by authorized personnel and that they are clearly documented and validated.

6.4 Other documents

Shipping and storage requirements should be established to ensure that the product reaches the manufacturer with proper quality attributes. This should be mutually agreed upon between the vendor and the purchaser and established prior to transportation of product.

Written procedures should be established and followed for maintenance of the equipment. All maintenance activities performed must be recorded; this may be in the form of a log, computer data base or other appropriate documentation, as long as the system can identify who was responsible for performing each function.

7. Good practices in production and quality control

7.1 Change control and process validation

Process changes may lead to changes in inherent product characteristics. Manufacturers should have a formal process change system in place, with written standard operating procedures covering such changes. Management of the change system should be assigned to an independent quality unit having responsibility and authority for final approval of process changes.

Manufacturers of excipients often produce laboratory or pilot batches. Scale-up to commercial production may involve several stages and data should be reviewed to demonstrate the adequacy of the scale-up process. Scale-up may introduce significant problems of consistency between batches. Pilot batches should serve as the basis for establishing in-process and finished product purity specifications.

Typically, manufacturers will generate reports that discuss the development and limitation of the manufacturing process. Summaries of such reports should be reviewed to determine if the plant is capable of producing the excipient. The reports serve as the basis for the validation of the manufacturing and control procedures, as well as the basic documentation to demonstrate that the process works consistently.

A document comprising scale-up data and describing the process reactions, operating parameters, purifications, impurities and key tests needed for process control should be written. A retrospective analysis of historical data (through statistical data and process capability data analysis) as well as the previous documentation will provide a good basis for validation.

7.2 Good practices in production

7.2.1 Prevention of cross-contamination

Potential for cross-contamination should be considered in the design of the manufacturing process and facility. The degree to which cross contamination should be minimized depends on the safety and intended use of the excipient.

The precautions taken to minimize cross-contamination should be appropriate to the conditions of the manufacturing facility and will take account of the range of materials manufactured. When the excipient product is initially recovered, it should be in a clean environment and not exposed to airborne contaminants, such as dust from other excipient or industrial chemicals. Typically, the damp product will be unloaded into clean, covered containers and transported for drying and other manipulations. These subsequent operations should be performed in separate areas or under controlled conditions because once dry, the excipient is more likely to contaminate its environment, including any surrounding products. The primary consideration is that the building and facilities should not contribute to an actual or potential contamination of the excipient.

The air handling systems at the site of manufacture should be designed to prevent cross-contamination. In dedicated areas processing the same excipient, it is permissible to recycle a portion of the exhaust air back into the same area. The adequacy of such a system of operation for multi-use areas, especially if several products are processed simultaneously, should be carefully analysed. In multi-use areas where several products are completely confined in closed vessels and piping systems, filtration of the supply air (combined fresh make-up air and recycled air) is acceptable if the conditions are consistent with other existing regulations (e.g. environmental, safety).

In those areas where the excipient is in a damp or moistened form, such as filter or centrifuge cake, and may be exposed to room air, filter efficiencies in the supply air system as low as 85 % may be adequate. In those areas where one or more of the products is being processed in a dry form, such filtration may not be enough to prevent cross contamination. In all cases, manufacturers should be able to demonstrate the adequacy of their air handling systems.

Excipient manufacturers should have a documented programme identifying all insecticides, pesticides, rodenticides and herbicides used at the site of manufacture. Adequate measures should be taken to prevent these agents contaminating the excipients.

7.2.2 In-process blending/mixing

Some processes require blending or mixing. Such in-process blending is acceptable provided it is adequately documented in batch production records. Examples include:

- Collection of multiple batches or continuous accumulation of batches with defined endpoint in a single holding tank (with a new batch number).
- Recycling material from one batch for further use in a subsequent batch.
- Repeated crystallizations of the same mother liquor for better yield of crystals.
- Collecting several centrifuge loads in a single drier/blender.

Incidental carry-over is another type of in-process mixing that frequently occurs. Examples include:

- Residue adhering to the wall of a micronizer used for milling the finished excipient.
- Residual layer of damp crystals remaining in a centrifuge bowl after discharge of the bulk of the crystals from a prior batch.
- Incomplete discharge of fluids, crystals or particles from a processing vessel upon transfer of the material to the next step in the process.

These residues are usually acceptable since clean-up between successive batches of the same excipient is not normally required during production. However, in the case of non-dedicated production units, complete cleaning procedures designed to prevent contamination that would alter the quality of the substance must be employed when changing from one excipient to another. Checking the effectiveness of these cleaning procedures may require the use of analytical testing for the substances involved.

In contrast to in-process blending and incidental carry-over discussed above, other blending operations should be directed towards achieving homogeneity of the finished excipient batch. Three areas in the processing of finished batches of an excipient which should be examined carefully and critically are:

- the final blending operation to produce the finished batch;
- the point in the process at which the batch number is assigned;
- the sampling procedure used to obtain the sample that is intended to be representative of the batch.

Blending of excipient batches to salvage adulterated material is not an acceptable practice.

Mother liquors containing recoverable amounts of excipients are frequently reused. Secondary recovery procedures for such excipients are acceptable, if the recovered excipient meets its specifications and if recovery procedures are indicated in batch production records. Secondary recovery procedures for reactants and intermediates are acceptable provided that the recovered materials meet suitable specifications.

7.2.3 Control of microbial contamination

The manufacture of sterile excipients for use in aseptic/sterile processing presents technical challenges. It is essential that adequately qualified and trained personnel be used to supervise and perform procedures associated with the manufacture of sterile excipients. The environment in which procedures are conducted, and the operators themselves, are significant potential sources of contamination in aseptic operations. Processes should be designed to minimize contact between excipient and the environment and operators. Those aseptic excipient operations which require considerable operator involvement must have adequate controls. Major potential problem areas include aseptic

removal of the excipient from centrifuges, manual transfer to drying trays and mills, and the inability to sterilize the drier. Not all equipment currently in use can be sterilized.

The excipient manufacturer must document the cleaning of critical processing equipment such as centrifuges and driers. Any manipulation of sterile excipients after sterilization must be performed as a validated aseptic process. This is particularly important for those excipients which are not further sterilized prior to packaging into final containers. In some instances, the compendia¹ monographs may specify that an excipient which does not meet parenteral grade standards must be labelled as not suitable for use in the preparation of injectable products.

Some manufacturers of non-sterile excipients use heat, gamma radiation and other methods to reduce the microbial burden. These methods are acceptable provided the manufacturer has shown that the product meets microbial requirements and that the process is under control within the manufacturer's specifications. Any procedure should be validated in accordance with recognized international standards to demonstrate that the process will produce the intended result. Post-production treatment of excipients should not be used as a substitute for attention to microbiological control during production.

A protected environment may be necessary to avoid microbial contamination or degradation caused by exposure to heat, air or light. The degree of protection required may vary depending on the stage of the process. Often, direct operator contact is involved in the unloading of centrifuge bags, transfer hoses (particularly those used to transfer powders), drying equipment and pumps, and equipment should be designed to minimize the possibility of contamination. The sanitary design of transfer and processing equipment should be evaluated. Those with moving parts should be assessed for the integrity of seals and other packing materials to avoid product contamination.

Special environments required by some processes must be monitored at all times to ensure product quality (e.g. inert atmosphere, protection from light). If interruptions in the special environment occur, adequate evidence must be provided that they have not compromised the quality of the excipient. Such environmental concerns become increasingly important after purification of the excipient has been completed.

The environment to which the excipient may be exposed should be similar to that used in the manufacture of the final dosage form. This is especially true in the case of excipients intended for parenteral dosage forms. For example, controlled areas may need to be established along with appropriate air quality classifications. Such areas should be serviced by suitable air handling systems and there should be adequate environmental monitoring programmes. Any manipulation of sterile excipient after sterilization must be performed as an aseptic process, using Class 100 air³ and other aseptic controls.

³ Good manufacturing practices for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 1, Section 17.3 (WHO Technical Report Series, No. 823).

7.2.4 Water systems/water quality

While drinking-water is used for many excipient processes, purified water is also widely used. Because of the well-known potential for microbial growth in deionizers and ultrafiltration or reverse-osmosis systems used to produce purified water, such systems must be properly validated and checked. Proper control methods include the establishment of water quality specifications and corresponding action levels, remedial action when microbial levels are exceeded, and adequate maintenance procedures such as regeneration and sanitation/ sterilization.

Appropriate specifications for chemical and microbial quality should be established and periodic testing conducted. Such specifications will vary depending on the process and the point in the process when the water is used. For example, in some cases, if the water is used in later processing steps such as for a final wash of the filter cake, or if the excipient is crystallized from an aqueous system, the water quality standards may need to be higher than normally specified for purified water. This is particularly important where the excipient's intended use is in parenteral dosage forms. The frequency of microbial and chemical testing of purified water depends on a variety of factors, including the test results and the point in the process (e.g. final wash in centrifuge) at which such water is used.

Most purified water and water for injection systems, including reverse-osmosis and ultrafiltration systems, have the potential for endotoxin contamination. If the final excipient is supposed to be pyrogen free or sterile, or will be used in preparing parenteral products, validation of the system to control endotoxins should be conducted and routine testing of the process water for endotoxins should be performed (preferably by the LAL (*Limulus amoebocyte lysate*) method).

7.2.5 Packaging operations

When the programme for packaging operations is being set up, particular attention should be given to minimizing the risk of crosscontamination, mix-ups, or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or the use of electronic surveillance.

7.2.6 Delivery

The manufacturer should arrange for the protection of the product after final inspection and testing. Where contractually agreed, this protection should include delivery to destination. Distribution records should be kept.

7.3 Good practices in quality control

7.3.1 General

The quality control unit, in addition to having the responsibility and authority to approve or reject all components, in-process materials, packaging materials and

finished excipients, and to review production records, etc., should also be responsible for approving or rejecting excipients manufactured, processed, packaged, or held under contract by another company, as well as for approving or rejecting all procedures, specifications and process changes having an effect on the quality of the excipient.

7.3.2 Control of starting materials

All starting materials must be tested or otherwise verified prior to use. Verification should include a certificate of analysis from the supplier and, wherever feasible, an identification test. There should be clear guidance or standard operating procedures established for the approval of each starting material.

Starting materials are usually subjected to an identity test and additional testing to confirm that they meet appropriate specifications. Some starting materials may not be acceptance tested by the manufacturer because of the hazards involved or other valid considerations. In such cases, quality certification for each batch from the vendor should be on file. There should always be some evidence of an attempt by the excipient manufacturer to establish identity, even if it is only a visual examination of containers, examination of labels, or recording of batch numbers from the labels.

7.3.3 In-process testing

In-process inspection and testing should be performed by monitoring the process or by actual sample analysis at defined locations and times. The results should conform to established process parameters or acceptable tolerances. Work instructions should delineate the procedure to follow and how to use the inspection and test data to control the process.

7.3.4 Quality records and retention samples

The manufacturer should establish and maintain procedures for identification, collection, indexing, filing, storage, maintenance and availability of quality records. Quality records should be maintained to demonstrate achievement of the required quality and the effective operation of the quality system. These data should include pertinent subcontractor quality records.

All quality records should be legible and identifiable to the product involved. Quality records should be stored and maintained in such a way that they are readily retrievable, in facilities that provide a suitable environment to minimize deterioration or damage and to prevent loss. Retention times of quality records should be established and recorded. Where agreed contractually, quality records should be made available for evaluation by the purchaser or the purchaser's representative for an agreed period.

All appropriate records relating to inspection and testing must be available for review. Where the process is continuously monitored, acknowledgement must be made of this and the results of the monitoring should be available.

Reserve samples of the released excipient should be retained for one year after the expiry or re-evaluation date, or for one year after distribution is complete. Sample size should be twice the amount required to perform release specification testing.

7.3.5 Stability studies

Many excipient products are very stable and may not require extensive testing to check stability. The stability of some excipients may be affected by undetected changes in starting material specifications, or subtle changes in manufacturing procedures. Excipients may also be shipped in a large variety of different packaging types that can affect their stability (e.g. metal and plastic drums, bags, plastic and glass bottles, bulk tankers).

Some excipients may be similar in chemical structure to other excipients, and some may be mixtures or blends of other excipients. These excipients may be very similar to others within a product group. Minor quantitative differences of some of the components may be the only significant variation from one product to another. For these excipients, a “model product” approach to assess the stability may be appropriate. Stability studies of this type should involve selection of several “model products” that would be expected to simulate the stability of the product group being assessed. This selection must be scientifically based. Data from stability studies of these “model products” can be used to determine the theoretical stability of similar products.

The full stability testing programme, when needed, usually contains the following features and takes into account historical data:

- The programme should be formalized in writing and ongoing studies should be reviewed at least annually.
- The programme should periodically include a sample from at least one commercial size batch.
- Stability samples should be stored in containers that approximate the primary market container. Simulations of all types of containers are not required, unless there are theoretical reasons to indicate that stability may be affected by container type.
- The samples should be stored under conditions similar to those recommended for the marketed excipient product.
- Additional samples may be stored under stress conditions (e.g. elevated temperature, light, humidity or freezing) if such conditions might reasonably be encountered during distribution and storage.
- Stability-indicating test methods should be used.
- Where stability of the excipient appears to be a significant issue in its use in pharmaceutical manufacturing, additional periodic testing of either the specific material or “model products” may have to be performed to

ensure that the expected stability does not significantly change with future batches. The frequency of testing should be determined by the impact that the excipient's stability may have on its usage.

7.3.6 Expiry/re-evaluation dating

Conducting a stability testing programme does not necessarily mean that expiry dates must be used. Where stability testing indicates a limited shelf-life, the label should declare an expiry date or indicate the need for re-evaluation testing at an appropriate interval to assure quality at time of use.

If the need for special storage conditions exists (e.g. protection from light, heat) such restrictions should be placed on the label.

7.3.7 Calibration of measuring and test equipment

All measuring and test equipment identified as being part of the quality system should be properly calibrated and maintained. This includes all in-process instruments identified as critical quality instruments, as well as test equipment used in the laboratory. The control programme should include the standardization or calibration of reagents, instruments, apparatus, gauges and recording devices at suitable intervals, in accordance with an established written programme containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event that accuracy and/or precision limits are not met. Reagents, instruments, apparatus, gauges and recording devices not meeting established specifications should not be used. Computer systems used to verify that the product conforms to specifications must be audited to ensure satisfactory performance in the laboratory.

3. WHO good manufacturing practices: specific medical products

3.1 WHO good manufacturing practices for sterile pharmaceutical products

Annex 2, WHO Technical Report Series, 1044, 2022 (revised)

Background

This document is a revision of *WHO good manufacturing practices for sterile pharmaceutical products*, previously published in the WHO Technical Report Series, No. 961, Annex 6, 2011.¹ The revision was done in collaboration with the European Union and the Pharmaceutical Inspection Co-operation Scheme (PIC/S). The harmonized text will benefit the national regulatory authorities and manufacturers and save resources, thus improving patients' access to quality medicines.

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¹ WHO good manufacturing practices for sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. WHO Technical Report Series No. 961, Annex 6. Geneva: World Health Organization; 2011 (<https://apps.who.int/iris/handle/10665/44079>).

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Abbreviations

APS	aseptic process simulation
BFS	blow-fill-seal
CCS	contamination control strategy
CFU	colony-forming unit
EDI	electrodeionization
FFS	form-fill-seal
GMP	good manufacturing practices
HEPA	high-efficiency particulate air
HVAC	heating, ventilation and air-conditioning
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PQS	pharmaceutical quality system
PUPSIT	pre-use post-sterilization integrity test
RABS	restricted access barrier system
SUS	single-use system
WFI	water for injection

1. Introduction and scope

The manufacture of sterile products covers a wide range of sterile product types (such as active substances, excipients, primary packaging materials and finished dosage forms), packed sizes (single unit and multiple units), processes (from highly automated systems to manual processes) and technologies (for example, biotechnology, small molecule manufacturing and closed systems). This guideline provides general guidance that should be used in the design and control of premises, equipment, utilities, systems and procedures used for the manufacture of all sterile products. The principles of quality risk management should be applied to ensure that microbial, particulate and endotoxin/pyrogen contamination is prevented in the final product.

The principles of quality risk management should be applied in all sections of this document and will not be referred to in specific paragraphs. Where specific limits, frequencies or ranges are reflected, these should be considered as a minimum requirement. They are referred to based on historical regulatory experience where issues that have been identified could impact the safety of products and patients.

The intent of this guideline is to provide guidance for the manufacture of sterile products. Some of the principles and guidance, such as contamination control strategy (CCS), design of premises, cleanroom classification, qualification, validation, monitoring and personnel gowning, may be used to support the manufacture of other products that are not intended to be sterile, such as certain liquids, creams, ointments and low bioburden biological intermediates, where the control and reduction of microbial, particulate and endotoxin/pyrogen contamination are considered important. Where a manufacturer elects to apply guidance in this document to non-sterile products, the manufacturer should clearly document which principles have been applied and acknowledge that compliance with those principles should be demonstrated.

2. Principle

- 2.1 The manufacture of sterile products is subject to specific requirements in order to minimize risks of microbial, particulate and endotoxin/pyrogen contamination. As a minimum, the following areas should be considered:
- i. Premises, equipment and process should be appropriately designed, qualified and validated and, where applicable, be subjected to ongoing verification according to the relevant sections of the good manufacturing practices (GMP) guide. The use of appropriate technologies (such as restricted access barrier systems (RABS), isolators, robotic systems, rapid/alternative methods and continuous monitoring systems) should be considered to increase the protection of the product from potential sources of endotoxin/pyrogen, particulate and microbial contamination, such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and the product.
 - ii. Personnel should have adequate qualifications, experience, and training. They should behave in a manner that ensures the protection of sterile product during the manufacturing, packaging and distribution processes.
 - iii. Processes and monitoring systems for sterile product manufacture should be designed, commissioned, qualified, monitored and regularly reviewed by personnel with appropriate process, engineering and microbiological knowledge and experience.
 - iv. Raw materials and packaging materials should be adequately controlled and tested for bioburden and endotoxin/pyrogen. These materials should meet their specification and should be suitable for use.
- 2.2 Processes, equipment, facilities and manufacturing activities should be managed in accordance with the principles of quality risk management to provide a

proactive means of identifying, scientifically evaluating and controlling potential risks to quality. Where alternative approaches are used, these should be supported by appropriate rationale and scientific justification. Quality risk management principles should cover the appropriate design of the facility, equipment and processes, as well as well designed procedures, and the application of monitoring systems that demonstrates that the design and procedures have been correctly implemented and continue to perform in line with expectations. Monitoring or testing alone does not give assurance of sterility.

- 2.3 A CCS should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organizational) and monitoring measures employed to manage risks to medicinal product quality. The combined strategy of the CCS should provide robust assurance of contamination prevention. The CCS should be reviewed periodically and, where appropriate, updated to drive continual improvement. Its effectiveness should be reviewed as part of the periodic management review process. Where existing control systems are in place and are appropriately managed, these may not require replacement but should be referenced in the CCS and the associated interactions between systems should be understood.
- 2.4 Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources should include a series of interrelated events and measures. These should be assessed and controlled and their effectiveness monitored individually and collectively.
- 2.5 The development of the CCS requires detailed technical and process knowledge. Potential sources of contamination are attributable to microbial and cellular debris (such as pyrogen or endotoxin) as well as particulate (such as glass and other visible and subvisible particles).

Elements to be considered within a CCS should include:

- i. design of both the entire plant and processes, including the associated documentation;
- ii. premises and equipment;
- iii. personnel;
- iv. utilities;
- v. raw material controls, including in-process controls;
- vi. product containers and closures;
- vii. vendor approval, for example key component suppliers, sterilization of components and single-use systems (SUS), and critical service providers;

- viii. management of outsourced activities and availability and transfer of critical information between parties, for example contract sterilization services;
 - ix. process risk management;
 - x. process validation;
 - xi. validation of sterilization processes;
 - xii. maintenance of equipment, utilities and premises (planned and unplanned maintenance);
 - xiii. cleaning and disinfection;
 - xiv. monitoring systems, including an assessment of the feasibility of the introduction of scientifically sound alternative methods that optimize the detection of environmental contamination;
 - xv. prevention mechanisms, including trend analysis, detailed investigation, root cause determination, corrective and preventive actions, and the need for comprehensive investigational tools;
 - xvi. continuous improvement.
- 2.6 The CCS should consider all aspects of contamination control, with ongoing and periodic review resulting in updates within the pharmaceutical quality system as appropriate. Changes to the systems in place should be assessed for any impact on the CCS before and after implementation.
- 2.7 The manufacturer should take all necessary steps and precautions to ensure the sterility of the products manufactured. Sole reliance for sterility or other quality aspects should not be placed on any terminal process or finished product testing.

3. Pharmaceutical quality system

- 3.1 The manufacturer's pharmaceutical quality system (PQS) should encompass and address the specific requirements of sterile product manufacture and ensure that all activities are effectively controlled so as to minimize the risk of microbial, particulate and endotoxin/pyrogen contamination. In addition to the PQS requirements detailed in the main text of the *WHO good manufacturing principles for pharmaceutical products: main principles*,² the PQS for sterile product manufacture should also ensure that:

² Annex 2 of WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. WHO Technical Report Series No. 986. Geneva: World Health Organization; 2014.

- i. An effective risk management system is integrated into all areas of the product life cycle with the aim of minimizing contamination and ensuring the quality of sterile products manufactured.
 - ii. The manufacturer has sufficient knowledge and expertise in relation to the products manufactured and the equipment, engineering and manufacturing methods employed that may have an impact on product quality.
 - iii. Root cause analysis of failures, including of procedure, process or equipment, is performed in such a way that the risk to product is correctly identified and understood, while ensuring that appropriate corrective and preventive actions are implemented.
 - iv. Risk management is applied in the development and maintenance of the CCS to identify, assess, reduce (or eliminate where possible) and control contamination risks. Risk management should be documented and should include the rationale for decisions taken in relation to risk reduction and acceptance of residual risk.
 - v. Senior management should effectively oversee the state of control throughout the facility and product life cycle. Risk management outcomes should be reviewed regularly as part of ongoing quality management, during change, in the event of a significant emerging problem, and during the periodic product quality review.
 - vi. Processes associated with the finishing, storage and transport of sterile products should not compromise the quality of the product. Aspects that should be considered include container integrity, risks of contamination, and avoidance of degradation by ensuring that products are stored and maintained in accordance with the registered storage conditions.
 - vii. Persons responsible for the certification or release of sterile products should have appropriate access to manufacturing and quality information and possess adequate knowledge and experience in the manufacture of sterile products and the associated critical quality attributes. This is in order to allow such persons to determine whether the sterile products have been manufactured in accordance with the registered specifications and approved process, and are of the required quality.
- 3.2 All non-conformities, such as sterility test failures, environmental monitoring excursions or deviations from established procedures, should be adequately investigated before certification or release of the batch. The investigation should determine the potential impact upon process and product quality and whether any other processes or batches are potentially impacted. The reason for including or excluding a product or batch from the scope of the investigation should be clearly justified and recorded.

4. Premises

- 4.1 The manufacture of sterile products should be carried out in appropriate cleanrooms, entry to which should be through change rooms that act as airlocks. Cleanrooms and change rooms should be maintained at an appropriate cleanliness standard and supplied with air that has passed through filters of an appropriate efficiency. Controls and monitoring should be scientifically justified and should effectively evaluate the state of environmental conditions of cleanrooms, airlocks and pass-through hatches.
- 4.2 The various operations of component preparation, product preparation and filling should be carried out with appropriate technical and operational separation measures within the cleanroom or facility to prevent mix-up and contamination.
- 4.3 RABS or isolators may be beneficial in assuring required conditions and minimizing microbial contamination associated with direct human interventions in the critical zone. Their use should be documented in the CCS. Any alternative approaches to the use of RABS or isolators should be justified.
- 4.4 Four grades of cleanrooms or zones are normally used for the manufacture of sterile products.

Grade A. This is the critical zone for high-risk operations (for example, aseptic processing line, filling zone, stopper bowl, open primary packaging, or for making aseptic connections under the protection of first air). Normally, such conditions are provided by a localized airflow protection, such as unidirectional airflow work stations within RABS or isolators. The maintenance of unidirectional airflow should be demonstrated and qualified across the whole of the grade A area. Direct intervention (for example, without the protection of barrier and glove port technology) into the grade A area by operators should be minimized by premises, equipment, process and procedural design.

Grade B. For aseptic preparation and filling, this is the background cleanroom for grade A (where it is not an isolator). Where applicable, air pressure differential between grade B and an adjacent area should be continuously monitored. Cleanrooms of lower grade than grade B can be considered where isolator technology is used (refer to paragraph 4.20).

Grades C and D. These are cleanrooms used for carrying out less critical stages in the manufacture of aseptically filled sterile products or as a background for isolators. They can also be used for the preparation or filling of terminally sterilized products (see section 8 for specific details on terminal sterilization activities).

- 4.5 In cleanrooms and critical zones, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or microorganisms.
- 4.6 To reduce accumulation of dust and to facilitate cleaning, there should be no recesses that are difficult to clean effectively. Projecting ledges, shelves, cupboards and equipment should be kept to a minimum. Doors should be designed to avoid recesses that cannot be cleaned. Sliding doors may be undesirable for this reason.
- 4.7 Materials used in cleanrooms, both in the construction of the room and for items used within the room, should be selected to minimize generation of particles. These should permit the repeated application of cleaning, disinfecting and sporicidal agents where used.
- 4.8 Ceilings should be designed and sealed to prevent contamination from the space above them.
- 4.9 Sinks and drains should be prohibited in the grade A and B areas. In other cleanrooms, air breaks should be fitted between the machine or sink and the drains. Floor drains in lower-grade cleanrooms should be fitted with traps or water seals designed to prevent backflow and should be regularly cleaned, disinfected and maintained.
- 4.10 The transfer of equipment and materials into and out of the cleanrooms and critical zones is one of the greatest potential sources of contamination. Any activities with the potential to compromise the cleanliness of cleanrooms or the critical zone should be assessed, and if they cannot be eliminated appropriate controls should be implemented.
- 4.11 The transfer of materials, equipment and components into the grade A or B areas should be carried out via a unidirectional process. Where possible, items should be sterilized and passed into these areas through double-ended sterilizers (for example, through a double-door autoclave or depyrogenation oven or tunnel) sealed into the wall. Where sterilization upon transfer of the items is not possible, a procedure that achieves the same objective of not introducing contamination should be validated and implemented (for example, using an effective transfer disinfection process, rapid transfer systems or ports for isolators, or, for gaseous or liquid materials, a bacteria-retentive filter). The removal of items from the grade A and B areas (such as materials, waste and environmental samples) should be carried out via a separate unidirectional process. If this is not possible, time-based separation of movement (incoming or exiting material) by procedure should be considered and controls applied to avoid potential contamination of incoming items.

4.12 Airlocks should be designed and used to provide physical separation and to minimize microbial and particle contamination of the different areas, and should be present for material and personnel moving between different grades. Wherever possible, airlocks used for personnel movement should be separated from those used for material movement. Where this is not practical, time-based separation of movement (personnel or material) by procedure should be considered. Airlocks should be effectively flushed with filtered air to ensure that the grade of the cleanroom is maintained. The final airlock should, in the at rest state, be of the same cleanliness grade (viable and total particle) as the cleanroom into which it leads. The use of separate change rooms for entering and leaving the grade B area is desirable. Where this is not practical, time-based separation of activities (inward or outward) by procedure should be considered. Where the CCS indicates that the risk of contamination is high, separate change rooms for entering and leaving production areas should be used. Airlocks should be designed as follows:

- i. Personnel airlocks: areas of increasing cleanliness used for entry of personnel (for example, from the grade D area to the grade C area to the grade B area). In general, handwashing facilities should be provided only in the first change room and should not be present in change rooms directly accessing the grade B area.
- ii. Material airlocks: used for materials and equipment transfer.
 - Only materials and equipment that have been included on an approved list and assessed during validation of the transfer process should be transferred into the grade A or B areas via an airlock or pass-through hatch. Equipment and materials intended for use in the grade A area should be protected when transiting through the grade B area. Any unapproved items that require transfer should be preapproved as an exception. Appropriate risk assessment and mitigation measures should be applied and recorded as per the manufacturer's CCS and should include a specific disinfection and monitoring programme approved by quality assurance.
 - Pass-through hatches should be designed to protect the higher-grade environment, for example by effective flushing with active filtered air supply of appropriate grade in accordance with the CCS.
 - The movement of material or equipment from lower-grade or unclassified areas to higher-grade clean areas should be subject to cleaning and disinfection commensurate with the risk and in line with the CCS.

4.13 For pass-through hatches and airlocks (for material and personnel), the entry and exit doors should not be opened simultaneously. For airlocks leading to the

grade A and B areas, an interlocking system should be used. For airlocks leading to grade C and D areas, a visual or audible warning system should be operated as a minimum. Where required to maintain area segregation, a time delay between the closing and opening of interlocked doors should be established and validated.

- 4.14 Cleanrooms should be supplied with a filtered air supply that maintains a positive pressure and an airflow relative to the background environment of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have an air pressure differential of a minimum of 10 pascals (guidance value). Particular attention should be paid to the protection of the critical zone. The recommendations regarding air supplies and air pressures may need to be modified where it is necessary to contain certain materials (such as pathogenic, highly toxic or radioactive products or live viral or bacterial materials). The modification may include positively or negatively pressurized airlocks that prevent the hazardous material from contaminating surrounding areas. Decontamination (for example, of the cleanrooms and the heating, ventilation and air-conditioning (HVAC) systems) and the treatment of air leaving a clean area may be necessary for some operations. Where containment requires air to flow into a critical zone, the source of the air should be an area of the same or higher grade.
- 4.15 Airflow visualization studies should demonstrate airflow patterns within cleanrooms and zones proving that there is no ingress from lower-grade to higher-grade areas and that air does not flow from less clean areas (such as the floor) or over operators or equipment, thus transferring contaminants to the higher-grade areas. Where unidirectional airflow is required, visualization studies should be performed to demonstrate compliance (refer to paragraphs 4.4 and 4.19). When filled and closed products are transferred to an adjacent cleanroom of a lower grade via a small exit point, airflow visualization studies should demonstrate that there is no ingress from the lower-grade cleanroom to the grade B area. Where air movement is shown to be a contamination risk to the clean area or critical zone, corrective action, such as design improvement, should be implemented. Airflow pattern studies should be performed both at rest and in operation (for example, simulating operator interventions). Video recordings of the airflow patterns should be carried out by following good practices to demonstrate the above. Recordings should be retained. The outcome of the air visualization studies should be documented and taken into consideration when establishing the facility's environmental monitoring programme.
- 4.16 Indicators of air pressure differential should be fitted between cleanrooms and between isolators and their background. Set points and the criticality of air pressure differential should be considered within the CCS. Air pressure differentials identified as critical should be continuously monitored and recorded. A warning

system should be in place to instantly indicate and warn operators of any failure in the air supply or reduction of air pressure differential (below set limits for those identified as critical). The warning signal should not be overridden without appropriate assessment and a procedure should be available to outline the steps to be taken when a warning signal is given. Where alarm delays are set, these should be assessed and justified within the CCS. Other air pressure differentials should be monitored and recorded at regular intervals.

- 4.17 Facilities should be designed to permit observation of production activities from outside the grade A and B areas (for example, through the provision of windows or remote cameras with a full view of the area and processes to enable observation and supervision without entry). This requirement should be considered when designing new facilities or during the refurbishment of existing facilities.

Barrier technologies

- 4.18 Isolators and RABS, which are different technologies, and the associated processes, should be designed to provide protection through separation of its grade A environment and the surrounding environment. The hazards introduced from entry or removal of items during processing should be minimized and supported by high-capability transfer technologies or validated systems that effectively prevent contamination and are appropriate for the respective technology.

- 4.19 The design of the technology and processes used should ensure that appropriate conditions are maintained in the critical zone to protect the exposed product during operations.

i. Isolators:

- a. The design of open isolators should ensure grade A conditions with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing.
- b. The design of closed isolators should ensure grade A conditions with adequate protection for exposed products during processing. Airflow may not be fully unidirectional in closed isolators where simple operations are conducted. However, any turbulent airflow should not increase the risk of contamination of the exposed product. Where processing lines are included in closed isolators, grade A conditions should be ensured with first air protection in the critical zone and unidirectional airflow that sweeps over and away from exposed products during processing.
- c. Negative pressure isolators should only be used when containment of the product is considered essential (for example, radiopharmaceutical

products) and specialized risk control measures should be applied to ensure the critical zone is not compromised.

ii. RABS:

- a. The design of RABS should ensure grade A conditions with unidirectional airflow and first air protection in the critical zone. A positive airflow from the critical zone to the supporting background environment should be maintained.

4.20 The background environment for isolators and RABS should ensure that the risk of transfer of contamination is minimized.

i. Isolators:

- a. The background environment for open isolators should generally correspond to a minimum of grade C. The background for closed isolators should correspond to a minimum of grade D. The decision on the background classification should be based on risk assessment and justified in the CCS.
- b. Key considerations when performing the risk assessment for the CCS of an isolator should include the biodecontamination programme, the extent of automation, the impact of glove manipulations that may potentially compromise first air protection of critical process points, the impact of potential loss of barrier or glove integrity, transfer mechanisms used, and activities such as set-up or maintenance that may require the doors to be opened prior to the final biodecontamination of the isolator. Where additional process risks are identified, a higher grade of background should be considered unless appropriately justified in the CCS.
- c. Airflow pattern studies should be performed at the interfaces of open isolators to demonstrate the absence of air ingress.

ii. RABS:

- a. The background environment for RABS used for aseptic processing should correspond to a minimum of grade B, and airflow pattern studies should be performed to demonstrate the absence of air ingress during interventions, including door openings if applicable.

4.21 The materials used for glove systems (for both isolators and RABS) should be demonstrated to have appropriate mechanical and chemical resistance. The frequency of glove replacement should be defined within the CCS.

i. Isolators:

- a. For isolators, leak testing of the glove system should be performed using a methodology demonstrated to be suitable for the task and criticality. The testing should be performed at defined intervals. Generally, glove integrity testing should be performed at a minimum frequency at the beginning and end of each batch or campaign. Additional glove integrity testing may be necessary, depending on the validated campaign length. Glove integrity monitoring should include a visual inspection associated with each use and following any manipulation that may affect the integrity of the system.
- b. For manual aseptic processing activities where single unit or small batch sizes are produced, the frequency of integrity verification may be based on other criteria, such as the beginning and end of each manufacturing session.
- c. Integrity and leak testing of isolator systems should be performed at defined intervals.

ii. RABS:

- a. For RABS, gloves used in the grade A area should be sterilized before installation and sterilized or effectively biodecontaminated by a validated method prior to each manufacturing campaign. If exposed to the background environment during operation, disinfection using an approved methodology following each exposure should be completed. Gloves should be visually examined with each use, and integrity testing should be performed at periodic intervals.

4.22 Decontamination methods (cleaning and biodecontamination, and where applicable inactivation for biological materials) should be appropriately defined and controlled. The cleaning process prior to the biodecontamination step is essential, as any residues that remain may inhibit the effectiveness of the decontamination process. Evidence should also be available to demonstrate that the cleaning and biodecontamination agents used do not have any adverse impact on the product produced within the RABS or isolator.

i. Isolators:

- a. The biodecontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (for example, gaseous or vaporized form). Gloves should be appropriately extended with fingers separated to ensure overall contact with the agent. Methods used

(cleaning and sporicidal biodecontamination) should render the interior surfaces and critical zone of the isolator free from viable microorganisms.

ii. RABS:

- a. The sporicidal disinfection should include the routine application of a sporicidal agent using a method that has been validated and demonstrated to effectively include all areas of the interior surfaces and ensure a suitable environment for aseptic processing.

Cleanroom and clean air equipment qualification

- 4.23 Cleanrooms and clean air equipment used for the manufacture of sterile products, such as unidirectional airflow units, RABS and isolators, should be qualified. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risk of contamination of the materials or product being handled. The appropriate cleanliness levels in the at rest and operational states should be maintained.
- 4.24 Cleanrooms and clean air equipment should be qualified using methodology in accordance with the requirements of the WHO *Good manufacturing practices: guideline on validation*.³ Cleanroom qualification (including classification) should be clearly differentiated from operational environmental monitoring.
- 4.25 Cleanroom and clean air equipment qualification is the overall process of confirming the level of compliance of a classified cleanroom or clean air equipment. As part of the qualification requirements, the qualification of cleanrooms and clean air equipment should include (where relevant to the design and operation of the installation):
- i. installed filter leakage test and filter integrity testing
 - ii. airflow tests – volume and velocity
 - iii. air pressure differential test
 - iv. airflow direction test and air flow visualization test
 - v. microbial airborne and surface contamination test
 - vi. temperature measurement test
 - vii. relative humidity test
 - viii. recovery test
 - ix. containment leakage test.

³ Annex 3 of WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. WHO Technical Report Series No. 1019. Geneva: World Health Organization; 2019.

Reference for the qualification of the cleanrooms and clean air equipment can be found in the *WHO Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products*⁴ and ISO 14644 series of standards.

- 4.26 Cleanroom classification is part of the cleanroom qualification and is a method of confirming the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the particle concentration. Classification activities should be scheduled and performed in order to avoid any impact on process or product quality. For example, initial classification should be performed during simulated operations and reclassification performed during simulated operations or during aseptic process simulation (APS).
- 4.27 For cleanroom classification, the total of particles equal to or greater than 0.5 and 5 µm should be measured. Maximum permitted particle concentration limits are specified in Table. 1.

Table. 1
Maximum permitted total particle concentration for classification

Grade	Maximum limits for total particle ≥ 0.5 µm/m³		Maximum limits for total particle ≥ 5 µm/m³	
	At rest	In operation	At rest	In operation
A	3 520	3 520	Not specified ^a	Not specified ^a
B	3 520	352 000	Not specified ^a	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined ^b	29 300	Not predetermined ^b

^a Classification including 5 µm particles may be considered where indicated by the CCS or historical trends.

^b For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and routine data where applicable.

- 4.28 For classification of the cleanroom, the minimum number of sampling locations and their positioning can be found in ISO 14644 Part 1. For the aseptic processing area and the background environment (the grade A and B areas, respectively) additional sample locations should be considered, and all critical processing areas,

⁴ Annex 8 of WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. WHO Technical Report Series No. 1010. Geneva: World Health Organization; 2018.

such as the point of fill and container closure feeder bowls, should be evaluated. Critical processing locations should be determined by documented risk assessment and knowledge of the process and operations to be performed in the area.

4.29 Cleanroom classification should be carried out in the at rest and in operation states.

- i. The definition of the at rest state is the condition whereby the installation of all the utilities is complete, including any functioning HVAC, with the main manufacturing equipment installed as specified but not operating and without personnel present in the room.
- ii. The definition of the in operation state is the condition whereby the installation of the cleanroom is complete, the HVAC system fully operational, and the equipment is installed and functioning in the manufacturer's defined operating mode, with the maximum number of personnel present performing or simulating routine operational work.
- iii. The total particle limits given in Table.1 above for the at rest state should be achieved after a clean-up period upon completion of operations and line clearance or cleaning activities. The clean-up period (guidance value of less than 20 minutes) should be determined during the qualification of the rooms, documented, and adhered to in procedures to reinstate a qualified state of cleanliness if disrupted during operation.

4.30 The speed of air supplied by unidirectional airflow systems should be clearly justified in the qualification protocol, including the location for air speed measurement. Air speed should be designed, measured and maintained to ensure that appropriate unidirectional air movement provides protection of the product and open components at the working position (for example, where high-risk operations occur and where product or components are exposed). Unidirectional airflow systems should provide a homogeneous air speed in a range of 0.36–0.54 metres per second (m/s) (guidance value) at the working level, unless otherwise scientifically justified in the CCS. Airflow visualization studies should correlate with the air speed measurement.

4.31 The microbial contamination level of the cleanrooms should be determined as part of the cleanroom qualification. The number of sampling locations should be based on a documented risk assessment and the results obtained from room classification, air visualization studies, and knowledge of the process and operations to be performed in the area. The maximum limits for microbial contamination during qualification for each grade are given in Table. 2. Qualification should include both at rest and operational states.

Table. 2**Maximum permitted microbial contamination level during qualification**

Grade	Air sample CFU/m ³	Settle plates (diameter 90 mm) CFU/4 hours ^a	Contact plates (diameter 55 mm) CFU/plate
A		No growth	
B	10	5	5
C	100	50	25
D	200	100	50

CFU = colony-forming unit.

^a Settle plates should be exposed for the duration of operations and changed as required, or after a maximum of 4 hours. Exposure time should be based on recovery studies and should not allow desiccation of the media used.

Note 1: All methods indicated for a specific grade in the table should be used for qualifying the area of that specific grade. If one of the methods tabulated is not used, or alternative methods are used, the approach taken should be appropriately justified.

Note 2: Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and where possible correlate them to CFU.

Note 3: For the qualification of personnel gowns, the limits given for contact plates and glove prints in Table.6 should apply.

Note 4: Sampling methods should not pose a risk of contamination to the manufacturing operations.

4.32 The requalification of cleanrooms and clean air equipment should be carried out periodically following defined procedures. The requalification should include, at a minimum, the following:

- i. cleanroom classification (total particle concentration);
- ii. integrity test of final filters;
- iii. airflow volume measurement;
- iv. verification of air pressure difference between rooms;
- v. air velocity test. Note: For grade B, C and D, the air velocity test should be performed according to a risk assessment documented as part of the CCS. It is however, required for filling zones supplied with unidirectional airflow (for example, when filling terminally sterilized products or background to grade A and RABS). For grades with non-unidirectional airflow, a recovery test should replace velocity testing.

The maximum time interval for requalification of grade A and B areas is 6 months.

The maximum time interval for requalification of grade C and D areas is 12 months.

Appropriate requalification consisting of at least the above tests should also be carried out following completion of remedial action implemented to rectify an out of compliance equipment or facility condition or after changes to equipment, facility or processes, as appropriate. The significance of a change requiring requalification should be determined through the change management process. Examples of changes requiring requalification include the following:

- i. interruption of air movement that affects the operation of the installation;
- ii. change in the design of the cleanroom or of the operational setting parameters of the HVAC system;
- iii. special maintenance that affects the operation of the installation (such as a change of final filters).

Disinfection

- 4.33 The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, cleaning to remove surface contamination should be performed prior to disinfection. Cleaning programmes should effectively remove disinfectant residues. More than one type of disinfecting agent should be employed to ensure that where they have different modes of action, their combined usage is effective against bacteria and fungi. Disinfection should include the periodic use of a sporicidal agent. Monitoring should be undertaken regularly in order to assess the effectiveness of the disinfection programme and to detect changes in types of microbial flora (for example, organisms resistant to the disinfection regime currently in use).
- 4.34 The disinfection process should be validated. Validation studies should demonstrate the suitability and effectiveness of disinfectants in the specific manner in which they are used and on the type of surface material, or representative material if justified, and should support the in-use expiry periods of prepared solutions.
- 4.35 Disinfectants and detergents used in grade A and B areas should be sterile. Disinfectants used in grade C and D areas may also be required to be sterile where determined in the CCS. Where the disinfectants and detergents are diluted or prepared by the sterile product manufacturer, this should be done in a manner to prevent contamination, and they should be monitored for microbial contamination. Dilutions should be kept in previously cleaned (and sterilized, where applicable) containers and should only be stored for the defined period. If the disinfectants and detergents are supplied ready-made, then results from certificates of analysis or conformance can be accepted, subject to successful completion of the appropriate vendor qualification.

- 4.36 Where fumigation or vapour disinfection (for example, vapour phase hydrogen peroxide) of cleanrooms and associated surfaces is used, the effectiveness of the fumigation agent and dispersion system should be validated.

5. Equipment

- 5.1 A detailed written description of the equipment design should be available (including process and instrumentation diagrams as appropriate). This should form part of the initial qualification documentation and be kept up to date.
- 5.2 Equipment monitoring requirements should be defined in user requirements specifications during early stages of development, and confirmed during qualification. Process and equipment alarm events should be acknowledged and evaluated for trends. The frequency at which alarms are assessed should be based on their criticality (with critical alarms reviewed immediately).
- 5.3 As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance, and repairs can be performed outside the cleanroom. If maintenance has to be performed in the cleanroom, and the required standards of cleanliness or asepsis cannot be maintained, then precautions such as restricting access to the work area to specified personnel and generation of clearly defined work protocols and maintenance procedures should be considered. Additional cleaning, disinfection and environmental monitoring should also be performed where appropriate. If sterilization of equipment is required, it should be carried out, wherever possible, after complete reassembly.
- 5.4 The validated cleaning procedure should be able to:
- i. remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used;
 - ii. minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection.
- 5.5 For aseptic processes, direct and indirect product contact parts should be sterilized. Direct product contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that do not contact the product but may come into contact with other sterilized surfaces, the sterility of which is critical to the overall product sterility (for example, sterilized items such as stopper bowls and guides, and sterilized components).
- 5.6 All equipment, such as sterilizers, air handling systems (including air filtration systems) and water systems, should be subject to qualification, monitoring and

planned maintenance. Upon completion of maintenance or repairs, their return to use should be approved.

- 5.7 Where unplanned maintenance of equipment critical to the sterility of the product is to be carried out, an assessment of the potential impact to the sterility of the product should be performed and recorded.
- 5.8 A conveyor belt should not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilized (for example, in a sterilizing tunnel).
- 5.9 Particle counters, including sampling tubing, should be qualified. The manufacturer's recommended specifications should be considered for tube diameter and bend radii. Tube length should typically be no longer than 1 m unless justified, and the number of bends should be minimized. Portable particle counters with a short length of sample tubing should be used for classification purposes. Isokinetic sampling heads should be used in unidirectional airflow systems. They should be oriented appropriately and positioned as close as possible to the critical location to ensure that samples are representative.

6. Utilities

- 6.1 The nature and extent of controls applied to utility systems should be commensurate with the risk to product quality associated with the utility. The impact should be determined through risk assessment and documented as part of the CCS.
- 6.2 In general, higher-risk utilities are those that:
 - i. directly contact product (for example, water for washing and rinsing, gases and steam for sterilization);
 - ii. contact materials that will ultimately become part of the product;
 - iii. contact surfaces that come into contact with the product;
 - iv. otherwise directly impact the product.
- 6.3 Utilities should be designed, installed, qualified, operated, maintained and monitored in a manner that ensures that the utility system functions as expected.
- 6.4 Results for critical parameters and critical quality attributes of high-risk utilities should be subject to regular trend analysis to ensure that system capabilities remain appropriate.
- 6.5 Records of utility system installation should be maintained throughout the system's life cycle. Such records should include current drawings and schematic diagrams,

construction material lists and system specifications. Typically, important information includes attributes such as:

- i. pipeline flow direction, slope, diameter and length
 - ii. tank and vessel details
 - iii. valves, filters, drains, sampling points and user points.
- 6.6 Pipes, ducts and other utilities should not be present in cleanrooms. If unavoidable, then they should be installed so that they do not create recesses, unsealed openings and surfaces that are difficult to clean. Installation should allow cleaning and disinfection of outer surface of the pipes.

Water systems

- 6.7 Note: Refer to WHO *Good manufacturing practices: water for pharmaceutical use* (Annex 3, WHO Technical Report Series 1033, 2021) and *Production of water for injection by means other than distillation* (Annex 3, WHO Technical Report Series 1025, 2020) for the main principles on water systems; and monographs for water for injection published in *The International Pharmacopoeia*, as well as various national pharmacopoeias for the minimum requirements for the quality of water for injection. Water treatment plant and distribution systems should be designed, constructed, installed, commissioned, qualified, monitored and maintained to prevent microbiological contamination and to ensure a reliable source of water of an appropriate quality. Measures should be taken to minimize the risk of presence of particulates, microbial contamination and proliferation, and endotoxin/pyrogen (for example, by sloping pipes to provide complete drainage and the avoidance of dead legs). Where filters are included in the system, special attention should be given to their monitoring and maintenance. Water produced should comply with the current monograph of the relevant pharmacopoeia.
- 6.8 Water systems should be qualified and validated to maintain the appropriate levels of physical, chemical and microbial control, taking the effect of seasonal variation into account.
- 6.9 Water flow should remain turbulent through the pipes in water distribution systems to minimize the risk of microbial adhesion and subsequent biofilm formation. The flow rate should be verified during qualification and be routinely monitored.
- 6.10 Water for injection (WFI)) should be produced from water meeting specifications that have been defined during the qualification process, stored and distributed in a manner that minimizes the risk of microbial growth (for example, by constant circulation at a temperature above 70 °C). WFI should be produced by distillation or other suitable means. These may include reverse osmosis coupled with other

appropriate techniques such as electrodeionization (EDI), ultrafiltration or nanofiltration.

- 6.11 Where storage tanks for water for pharmaceutical use and WFI are equipped with hydrophobic bacteria-retentive vent filters, the filters should not be a source of contamination and the integrity of the filter should be tested before installation and after use. Controls should be in place to prevent condensation formation on the filter (for example, heating).
- 6.12 To minimize the risk of biofilm formation, sterilization, sanitization, disinfection or regeneration, as appropriate, of water systems should be carried out according to a predetermined schedule and as a remedial action following out-of-limit or specification results. Disinfection of a water system with chemicals should be followed by a validated rinsing or flushing procedure. Water should be tested after disinfection or regeneration. Chemical testing results should be approved before the water system is returned to use and microbiological (endotoxin, where appropriate) results verified to be within specification and approved before batches manufactured using water from the system are considered for certification or release.
- 6.13 Regular ongoing chemical and microbial monitoring of water systems should be performed to ensure that the water continues to meet compendial expectations. Alert levels should be based on the initial qualification data and thereafter periodically reassessed on data obtained during subsequent requalifications, routine monitoring and investigations. The review of ongoing monitoring data should be carried out to identify any adverse trend in system performance. Sampling programmes should reflect the requirements of the CCS and should include all outlets and points of use, at a specified interval, to ensure that representative water samples are obtained for analysis on a regular basis. Sample plans should be based on the qualification data, should consider the potential worst-case sampling locations and should ensure that at least one representative sample is included every day of the water that is used for manufacturing processes.
- 6.14 Alert level excursions should be documented and reviewed, and include an investigation to determine whether the excursion is a single (isolated) event or if results are indicative of an adverse trend or system deterioration. Each action limit excursion should be investigated to determine the probable root causes and any potential impact on the quality of product and manufacturing processes as a result of the use of the water.
- 6.15 WFI systems should include continuous monitoring systems, for example for total organic carbon and conductivity, as these may give a better indication of overall system performance than discrete sampling. Sensor locations should be based on risk.

Steam used as a direct sterilizing agent

- 6.16 Feed water to a pure steam (clean steam) generator should be appropriately purified. Pure steam generators should be designed, qualified and operated in a manner that ensures that the quality of steam produced meets defined chemical and endotoxin levels.
- 6.17 Steam used as a direct sterilizing agent should be of suitable quality and should not contain additives at a level that could cause contamination of product or equipment. For a generator supplying pure steam used for the direct sterilization of materials or product contact surfaces (such as porous hard-good autoclave loads), steam condensate should meet the current monograph for WFI of the relevant pharmacopoeia (microbial testing is not mandatory for steam condensate). A suitable sampling schedule should be in place to ensure that the sample for analysis is collected on a regular basis. The sample should be representative of the pure steam. Other aspects of the quality of pure steam used for sterilization should be assessed periodically against parameters. These parameters should include the following (unless otherwise justified): non-condensable gases, dryness value (dryness fraction) and superheat.

Gases and vacuum systems

- 6.18 Gases that come in direct contact with the product or primary container surfaces should be of appropriate chemical, particulate and microbial quality. All relevant parameters, including oil and water content, should be specified, taking into account the use and type of the gas and the design of the gas generation system, and, where applicable, should comply with the current monograph of the relevant pharmacopoeia or the product quality requirement.
- 6.19 Gases used in aseptic processes should be filtered through a sterilizing grade filter (with a nominal pore size of a maximum of 0.22 µm) at the point of use. Where the filter is used on a batch basis (for example, for filtration of gas used for overlay of aseptically filled products) or as product vessel vent filter, then the filter should be integrity tested and the results reviewed as part of the batch certification and release process. Any transfer pipework or tubing that is located after the final sterilizing grade filter should be sterilized. When gases are used in the process, microbial monitoring of the gas should be performed periodically at the point of use.
- 6.20 Where backflow from vacuum or pressure systems poses a potential risk to the product, there should be a mechanism to prevent backflow when the vacuum or pressure system is shut off.

Heating and cooling and hydraulic systems

- 6.21 Major items of equipment associated with hydraulic, heating and cooling systems should, where possible, be located outside the filling room. There should be appropriate controls to contain any spillage or cross-contamination associated with the system fluids.
- 6.22 Any leaks from these systems that would present a risk to the product should be detectable (for example, using an indication system for leakage).

7. Personnel

- 7.1 The manufacturer should ensure that there is a sufficient number of personnel, appropriately and suitably qualified, trained and experienced in the manufacture and testing of sterile products, and any of the specific manufacturing technologies used in the site's manufacturing operations.
- 7.2 Only the minimum number of personnel required should be present in cleanrooms. The maximum number of operators in cleanrooms should be determined, documented and considered during activities, such as initial qualification and APS, so as not to compromise sterility assurance.
- 7.3 Personnel, including those performing cleaning, maintenance and monitoring and those that access cleanrooms, should receive regular training and undergo gowning qualification and assessment in disciplines relevant to the correct manufacture of sterile products. This training should include the basic elements of microbiology and hygiene (with a specific focus on cleanroom practices), contamination control, aseptic techniques and the protection of sterile products (for those operators entering the grade B cleanrooms or intervening into grade A), and the potential safety implications for the patient if the product is not sterile. The level of training should be based on the criticality of the function and area in which the personnel are working.
- 7.4 The personnel accessing grade A and B areas should be trained for aseptic gowning and aseptic behaviours. Compliance with aseptic gowning procedures should be confirmed by assessment and periodic reassessment at least annually, and should involve both visual and microbial assessment using monitoring locations such as gloved fingers, forearms, chest and hood (face mask and forehead) (refer to paragraph 9.30 for the expected limits). Unsupervised access to the grade A and grade B areas where aseptic operations are or will be conducted should be restricted to appropriately qualified personnel, who have passed the gowning assessment and have participated in a successful APS.

- 7.5 Unqualified persons should not enter grade B cleanrooms or grade A when in operation. If needed in exceptional cases, manufacturers should establish written procedures outlining the process by which unqualified persons are brought into the grade B and A areas. An authorized person from the manufacturer should supervise the unqualified persons during their activities and should assess the impact of these activities on the cleanliness of the area. Access by these persons should be assessed and recorded in accordance with the PQS.
- 7.6 There should be systems in place for the disqualification of personnel from working in or given unsupervised entry into cleanrooms that is based on specified aspects, including ongoing assessment or identification of an adverse trend from the personnel monitoring programme or implication in a failed APS. Once disqualified, retraining and requalification should be completed before permitting the operator to have any further involvement in aseptic practices. For operators entering grade B cleanrooms or performing intervention into grade A, this requalification should include consideration of participation in a successful APS.
- 7.7 High standards of personal hygiene and cleanliness are essential to prevent excessive shedding or increased risk of introduction of microbial contamination. Personnel involved in the manufacture of sterile products should be instructed to report any specific health conditions or ailments that may cause the shedding of abnormal numbers or types of contaminants and therefore preclude cleanroom access. Health conditions and actions to be taken with regard to personnel who could be introducing an undue microbial hazard should be provided by the designated competent person and described in procedures.
- 7.8 Personnel who have been engaged in the processing of human or animal tissue materials or of cultures of microorganisms, other than those used in the current manufacturing process, or any activities that may have a negative impact on quality (such as microbial contamination), should not enter clean areas unless clearly defined and effective decontamination and entry procedures have been followed and documented.
- 7.9 Wristwatches, make-up, jewellery, mobile phones and any other non-essential items should not be allowed in clean areas. Electronic devices used in cleanrooms (such as mobile phones and tablets) that are supplied by the manufacturer solely for use in the cleanrooms may be acceptable if suitably designed to permit cleaning and disinfection commensurate with the grade in which they are used. The use and disinfection of such equipment should be included in the CCS.
- 7.10 Cleanroom gowning and handwashing should follow a written procedure designed to minimize contamination of cleanroom clothing or the transfer of contaminants to the clean areas.

7.11 The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination. When the type of clothing chosen needs to provide the operator protection from the product, it should not compromise the protection of the product from contamination. Garments should be visually checked for cleanliness and integrity immediately prior to and after gowing. Gown integrity should also be checked upon exit. For sterilized garments and eye coverings, particular attention should be given to ensuring that they have been subject to the sterilization process and are within their specified hold time. The packaging should be visually inspected to ensure its integrity before use. Reusable garments (including eye coverings) should be replaced if damage is identified, and at a set frequency that is determined during qualification studies. The qualification of garments should consider any necessary garment testing requirements, including damage to garments that may not be identified by visual inspection alone.

7.12 Clothing should be chosen to limit shedding due to operators' movement.

7.13 A description of typical clothing required for each cleanliness grade is given below.

- i. **Grade B** (including access or interventions into grade A). Appropriate garments that are dedicated for use under a sterilized suit should be worn before gowing (refer to paragraph 7.14). Appropriately sterilized, non-powdered, rubber or plastic gloves should be worn while donning the sterilized garments. Sterile headgear should enclose all hair (including facial hair) and, where separate from the rest of the gown, should be tucked into the neck of the sterile suit. A sterile face mask and sterile eye coverings (such as goggles) should be worn to cover and enclose all facial skin and prevent the shedding of droplets and particles. The appropriate sterilized footwear (such as overboots) should be worn. Trouser legs should be tucked inside the footwear. Garment sleeves should be tucked into a second pair of sterile gloves worn over the pair worn while donning the gown. The protective clothing should minimize shedding of fibres and other particles and retain particles shed by the body. The particle shedding and the particle retention efficiencies of the garments should be assessed during the garment qualification. Garments should be packed and folded in such a way as to allow operators to don the gown without contacting the outer surface of the garment and to prevent the garment from touching the floor.
- ii. **Grade C**. Hair, beards and moustaches should be covered. A single- or two-piece trouser suit gathered at the wrists and with high neck and appropriately disinfected shoes or overshoes should be worn. They should minimize the shedding of fibres and particles.

- iii. **Grade D.** Hair, beards and moustaches should be covered. A general protective suit and appropriately disinfected shoes or overshoes should be worn. The appropriate measures should be taken to avoid any ingress of contaminants from outside the clean area.
 - iv. Additional gowning, including gloves and a face mask, may be required in grade C and D areas when performing activities considered to be a contamination risk, as defined by the CCS.
- 7.14 Cleanroom gowning should be performed in change rooms of an appropriate cleanliness grade to ensure that gown cleanliness is maintained. Outdoor clothing, including socks (other than personal underwear), should not be brought into changing rooms leading directly to grade B and C areas. Single- or two-piece facility trouser suits, covering the full length of the arms and the legs, and facility socks covering the feet should be worn before entry to change rooms for grades B and C. Facility suits and socks should not present a risk of contamination to the gowning area or processes.
- 7.15 Every operator entering grade B or A areas should gown into clean, sterilized protective garments (including eye coverings and masks) of an appropriate size at each entry. The maximum period for which the sterilized gown may be worn before replacement during a shift should be defined as part of the garment qualification.
- 7.16 Gloves should be regularly disinfected during operations. Garments and gloves should be changed immediately if they become damaged and present any risk of product contamination.
- 7.17 Reusable clean area clothing should be cleaned in a laundry facility adequately segregated from production operations, using a qualified process ensuring that the clothing is not damaged or contaminated by fibres or particles during the repeated laundry process. Laundry facilities used should not introduce risk of contamination or cross-contamination. The inappropriate handling and use of clothing may damage fibres and increase the risk of shedding of particles. After washing and before packing, garments should be visually inspected for damage and visual cleanliness. The garment management processes should be evaluated and determined as part of the garment qualification programme and should include a maximum number of laundry and sterilization cycles.
- 7.18 Activities in clean areas that are not critical to the production processes should be kept to a minimum, especially when aseptic operations are in progress. The movement of personnel should be slow, controlled and methodical to avoid excessive shedding of particles and organisms due to overvigorous activity. Operators performing aseptic operations should adhere to aseptic technique at all

times to prevent changes in air currents that may introduce air of lower quality into the critical zone. Movement adjacent to the critical zone should be restricted and obstruction of the path of the unidirectional (first air) airflow should be avoided. A review of airflow visualization studies should be considered as part of the training programme.

8. Production and specific technologies

Terminally sterilized products

- 8.1 Preparation of components and materials should be performed in at least a grade D cleanroom in order to limit the risk of microbial, endotoxin/pyrogen and particle contamination, so that the product is suitable for sterilization. Where the product is at a high or unusual risk of microbial contamination (for example, the product actively supports microbial growth and must be held for long periods before filling, or the product is not processed mostly in closed vessels), then preparation should be carried out in at least a grade C environment. The preparation of ointments, creams, suspensions and emulsions should be carried out in at least a grade C environment before terminal sterilization.
- 8.2 Primary packaging containers and components should be cleaned using validated processes to ensure that particle, endotoxin/pyrogen and bioburden contamination is appropriately controlled.
- 8.3 The filling of products for terminal sterilization should be carried out in at least a grade C environment.
- 8.4 Where the CCS identifies that the product is at an unusual risk of contamination from the environment – for example, when the filling operation is slow or when the containers are wide necked or are necessarily exposed for more than a few seconds before closing – then the product should be filled in grade A with at least a grade C background.
- 8.5 The processing of the bulk solution should include a filtration step with a microorganism-retaining filter, where possible, to reduce bioburden levels and particles prior to filling into the final product containers. The maximum permissible time between preparation and filling should be defined.
- 8.6 Examples of operations to be carried out in the various grades are given in Table 3.

Table. 3**Examples of operations and grades for terminally sterilized preparation and processing operations**

Grade	Operation
Grade A	<ul style="list-style-type: none"> • Filling of products, when unusually at risk
Grade C	<ul style="list-style-type: none"> • Preparation of solutions, when unusually at risk • Filling of products
Grade D	<ul style="list-style-type: none"> • Preparation of solutions and components for subsequent filling

Aseptic preparation and processing

- 8.7 The aseptic process should be clearly defined. The risks associated with the aseptic process, and any associated requirements, should be identified, assessed and appropriately controlled. The site's CCS should clearly define the acceptance criteria for these controls, requirements for monitoring and the review of their effectiveness. Methods and procedures to control these risks should be described and implemented. Accepted residual risks should be formally documented.
- 8.8 Precautions to minimize microbial, endotoxin/pyrogenic and particle contamination should be taken, as per the site's CCS, during the preparation of the aseptic environment, during all processing stages (including the stages before and after bulk product sterilization), and until the product is sealed in its final container. The presence of materials liable to generate particles and fibres should be minimized in cleanrooms.
- 8.9 Where possible, the use of equipment such as RABS, isolators or other systems should be considered in order to reduce the need for critical interventions into grade A and to minimize the risk of contamination. Robotics and automation of processes can also be considered to eliminate direct human critical interventions (for example, dry heat tunnel, automated lyophilizer loading, sterilization in place).
- 8.10 Examples of operations to be carried out in the various environmental grades are given in Table. 4.

Table. 4**Examples of operations and grades for aseptic preparation and processing operations**

Grade	Operation
Grade A	<ul style="list-style-type: none"> • Aseptic assembly of filling equipment • Connections made under aseptic conditions (where sterilized product contact surfaces are exposed) that are post the final sterilizing grade filter; these connections should be sterilized by steam-in-place whenever possible • Aseptic compounding and mixing • Replenishment of sterile bulk product, containers and closures • Removal and cooling of unprotected (e.g. with no packaging) items from sterilizers • Staging and conveying of sterile primary packaging components in the aseptic filling line while not wrapped • Aseptic filling, sealing of containers such as ampoules, vial closure, transfer of open or partially stoppered vials • Loading of a lyophilizer
Grade B	<ul style="list-style-type: none"> • Background support for grade A (when not in an isolator) • Conveying or staging, while protected from the surrounding environment, of equipment, components and ancillary items for introduction into grade A
Grade C	<ul style="list-style-type: none"> • Preparation of solutions to be filtered, including sampling and dispensing
Grade D	<ul style="list-style-type: none"> • Cleaning of equipment • Handling of components, equipment and accessories after cleaning • Assembly under high-efficiency particulate air (HEPA)-filtered airflow of cleaned components, equipment and accessories prior to sterilization • Assembly of closed and sterilized SUS using intrinsic sterile connection devices

8.11 For sterile products where the final formulation cannot be filtered, the following should be considered:

- i. All product and component contact equipment should be sterilized prior to use.
- ii. All raw materials or intermediates should be sterilized and aseptically added.
- iii. Bulk solutions or intermediates should be sterilized.

- 8.12 The unwrapping, assembly and preparation of sterilized equipment, components and ancillary items with direct or indirect product contact should be treated as an aseptic process and performed in grade A with a grade B background. The filling line set-up and filling of the sterile product should be treated as an aseptic process and performed in grade A with a grade B background. Where an isolator is used, the background should be in accordance with paragraph 4.20.
- 8.13 Preparation and filling of sterile products such as ointments, creams, suspensions and emulsions should be performed in grade A with a grade B background when the product and components are exposed to the environment and the product is not subsequently filtered (via a sterilizing grade filter) or terminally sterilized. Where an isolator or RABS is used, the background should be in accordance with paragraph 4.20.
- 8.14 Aseptic connections should be performed in grade A with a grade B background unless subsequently sterilized in place or conducted with intrinsic sterile connection devices that minimize any potential contamination from the immediate environment. Intrinsic sterile connection devices should be designed to mitigate risk of contamination.

Where an isolator is used, the background should be in accordance with paragraph 4.20. Aseptic connections should be appropriately assessed and their effectiveness verified (for requirements regarding intrinsic sterile connection devices, refer to paragraphs 8.129 and 8.130).

- 8.15 Aseptic manipulations (including non-intrinsic sterile connection devices) should be minimized through the use of engineering design solutions such as preassembled and sterilized equipment. Whenever feasible, product contact piping and equipment should be preassembled and sterilized in place.
- 8.16 There should be an authorized list of allowed and qualified interventions, both inherent and corrective, that may occur during production (refer to paragraph 9.34). Interventions should be carefully designed to ensure that the risk of contamination of the environment, process and product is effectively minimized. The process of designing interventions should include the consideration of any impact on airflows and critical surfaces and products. Engineering solutions should be used whenever possible to minimize incursion by operators during the intervention. Aseptic technique should be observed at all times, including the appropriate use of sterile tools for manipulations. The procedures listing the types of inherent and corrective interventions, and how to perform them, should be first evaluated via risk management and APS and should be kept up to date. Non-qualified interventions should only be used in exceptional circumstances, with due consideration of the risks associated with the intervention and with

the authorization of the quality unit. The details of the intervention conducted should be subject to risk assessment, recorded and fully investigated under the manufacturer's PQS. Any non-qualified interventions should be thoroughly assessed by the quality department and considered during batch disposition.

- 8.17 Interventions and stoppages should be recorded in the batch record. Each line stoppage or intervention should be sufficiently documented in batch records with the associated time, duration of the event, and operators involved (refer to paragraph 9.34).
- 8.18 The duration of each aspect of aseptic preparation and processing should be minimized and limited to a defined and validated maximum time, including:
- i. the holding time between equipment, component, and container cleaning, drying and sterilization;
 - ii. the holding time for sterilized equipment, components, and containers before use and during filling or assembly;
 - iii. the holding time for a decontaminated environment, such as the RABS or isolator before use;
 - iv. the time between the start of the preparation of a product and its sterilization or filtration through a microorganism-retaining filter (if applicable), through to the end of the aseptic filling process (there should be a maximum permissible time defined for each product that takes into account its composition and the prescribed method of storage);
 - v. the holding time for sterilized product prior to filling;
 - vi. the aseptic processing time;
 - vii. the filling time.
- 8.19 Aseptic operations (including APS) should be monitored on a regular basis by personnel (independent from the aseptic operation) with specific expertise in aseptic processing to verify the correct performance of operations, including operator behaviour in the cleanroom, and to address inappropriate practices if detected. Records should be maintained.

Finishing of sterile products

- 8.20 Open primary packaging containers should be maintained under grade A conditions with the appropriate background for the technology, as described in paragraph 4.20 (for partially stoppered vials or prefilled syringes, refer to paragraph 8.126).
- 8.21 Filled containers should be closed by appropriately validated methods.

- 8.22 Where filled containers are closed by fusion – for example, blow-fill-seal (BFS), form-fill-seal (FFS), or small- or large-volume parenteral bags, glass or plastic ampoules – the critical parameters and variables that affect seal integrity should be evaluated, determined, effectively controlled and monitored during operations. Glass ampoules, BFS units and small-volume containers (≤ 100 mL) closed by fusion should be subject to 100% integrity testing using validated methods. For large-volume containers (> 100 mL) closed by fusion, reduced sampling may be acceptable where scientifically justified and based on data demonstrating the consistency of the existing process, and a high level of process control. Visual inspection is not an acceptable integrity test method.
- 8.23 Samples of products using systems other than fusion should be taken and checked for integrity using validated methods. The frequency of testing should be based on the knowledge and experience of the container and closure systems being used. A scientifically justified sampling plan should be used. The sample size should be based on information such as supplier qualification, packaging component specifications and process knowledge.
- 8.24 Containers sealed under vacuum should be tested for maintenance of vacuum after an appropriate predetermined period prior to certification and release and during shelf life.
- 8.25 The container closure integrity validation should take into consideration any transportation or shipping requirements that may negatively impact the integrity of the container (for example, by decompression or extreme temperatures).
- 8.26 Where the equipment used to crimp vial caps can generate large quantities of non-viable particle, measures to prevent particle contamination, such as locating the equipment at a physically separate station equipped with adequate air extraction, should be taken.
- 8.27 Vial capping of aseptically filled products can be undertaken as an aseptic process using sterilized caps or as a clean process outside the aseptic processing area. Where the latter approach is adopted, vials should be protected by grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a grade A air supply until the cap has been crimped. The supporting background environment of grade A air supply should meet at least grade D requirements. Where capping is a manual process, it should be performed under grade A conditions either in an appropriately designed isolator or in grade A with a grade B background.
- 8.28 Where capping of aseptically filled sterile product is conducted as a clean process with grade A air supply protection, vials with missing or displaced stoppers should

be rejected prior to capping. Appropriately qualified, automated methods for stopper height detection should be in place.

- 8.29 Where human intervention is required at the capping station, appropriate technological and organizational measures should be used to prevent direct contact with the vials and to minimize contamination. RABS and isolators may be beneficial in assuring the required conditions.
- 8.30 All filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. Defect classification and criticality should be determined during qualification and based on risk and historical knowledge. Factors to consider include the potential impact of the defect on the patient and the route of administration. Different defect types should be categorized and batch performance analysed. Batches with unusual levels of defects, when compared with routine defect numbers for the process (based on routine and trend data), should be investigated. A defect library should be generated and maintained that captures all known classes of defects. The defect library should be used for the training of production and quality assurance personnel. Critical defects should not be identified during any subsequent sampling and inspection of acceptable containers. Any critical defect identified subsequently should trigger an investigation, as it indicates a possible failure of the original inspection process.
- 8.31 When inspection is performed manually, it should be conducted under suitable and controlled conditions of illumination and background. Inspection rates should be appropriately controlled and qualified. Operators performing the inspection should undergo visual inspection qualification (whilst wearing corrective lenses, if these are normally worn) at least annually. The qualification should be undertaken using appropriate samples from the manufacturer's defect library sets and taking into consideration worst-case scenarios (such as inspection time, line speed where the product is transferred to the operator by a conveyor system, container size and operator fatigue) and should include consideration of eyesight checks. Operator distractions should be minimized and frequent breaks of an appropriate duration should be taken from inspection.
- 8.32 Where automated methods of inspection are used, the process should be validated to detect known defects (which may impact product quality or safety) and be equal to, or better than, manual inspection methods. The performance of the equipment should be challenged using representative defects prior to start-up and at regular intervals throughout the batch.
- 8.33 The results of the inspection should be recorded and defect types and numbers trended. The reject levels for the various defect types should also be trended

based on statistical principles. The impact to the product on the market should be assessed as part of the investigation when adverse trends are observed.

Sterilization

- 8.34 Where possible, the finished product should be terminally sterilized, using a validated and controlled sterilization process, as this provides greater assurance of sterility than a validated and controlled sterile filtration process and/or aseptic processing. Where it is not possible for a product to undergo terminal sterilization, consideration should be given to using post-aseptic processing terminal heat treatment, combined with an aseptic process to give improved sterility assurance.
- 8.35 The selection, design and location of the equipment and cycle or programme used for sterilization should be based on scientific principles and data that demonstrate repeatability and reliability of the sterilization process. All parameters should be defined and, where critical, these should be controlled, monitored and recorded.
- 8.36 All sterilization processes should be validated. Validation studies should take into account the product composition, storage conditions and maximum time between the start of the preparation of a product or material to be sterilized and its sterilization. Before any sterilization process is adopted, its suitability for the product and equipment, and its efficacy in consistently achieving the desired sterilizing conditions in all parts of each type of load to be processed, should be validated – notably by physical measurements and, where appropriate, by biological indicators. For effective sterilization, the whole of the product and surfaces of equipment and components should be subject to the required treatment, and the process should be designed to ensure that this is achieved.
- 8.37 Particular attention should be given when the adopted product sterilization method is not described in the current edition of the pharmacopoeia, or when it is used for a product that is not a simple aqueous solution. Where possible, heat sterilization is the method of choice.
- 8.38 Validated loading patterns should be established for all sterilization processes and load patterns should be subject to periodic revalidation. Maximum and minimum loads should also be considered as part of the overall load validation strategy.
- 8.39 The validity of the sterilizing process should be reviewed and verified at scheduled intervals based on risk. Heat sterilization cycles should be revalidated with a minimum frequency of at least annually for load patterns that are considered worst case. Other load patterns should be validated at a frequency justified in the CCS.

- 8.40 Routine operating parameters should be established and adhered to for all sterilization processes (for example, physical parameters and loading patterns).
- 8.41 There should be mechanisms in place to detect a sterilization cycle that does not conform to the validated parameters. Any failed sterilization or sterilization that deviates from the validated process (for example, having longer or shorter phases such as heating cycles) should be investigated.
- 8.42 Suitable biological indicators placed at appropriate locations should be considered as an additional method to support the validation of the sterilization process. Biological indicators should be stored and used according to the manufacturer's instructions. Where biological indicators are used to support validation or to monitor a sterilization process (for example, with ethylene oxide), positive controls should be tested for each sterilization cycle. If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination to the manufacturing or other testing processes. Biological indicator results in isolation should not be used to override other critical parameters and process design elements.
- 8.43 The reliability of biological indicators is important. Suppliers should be qualified and transportation and storage conditions should be controlled in order that biological indicator quality is not compromised. Prior to use of a new batch or lot of biological indicators, the population, purity and identity of the indicator organism of the batch or lot should be verified. For other critical parameters (such as D-value or Z-value), the batch certificate provided by the qualified supplier can normally be used.
- 8.44 There should be a clear means of differentiating products, equipment and components that have not been subjected to the sterilization process from those that have. Equipment, such as baskets or trays used to carry products and other items of equipment or components, should be clearly labelled (or electronically tracked) with the product name and batch number and an indication as to whether or not it has been sterilized. Indicators – such as autoclave tape or irradiation indicators – may be used, where appropriate, to indicate whether or not a batch (or sub-batch material, component or equipment) has passed through a sterilization process. These indicators show only that the sterilization process has occurred; they do not indicate product sterility or achievement of the required sterility assurance level.
- 8.45 Sterilization records should be available for each sterilization run. Each cycle should have a unique identifier. Their conformity should be reviewed and approved as part of the batch certification or release procedure.

- 8.46 Where required, materials, equipment and components should be sterilized by validated methods appropriate to the specific material. Suitable protection after sterilization should be provided to prevent recontamination. If sterilized items are not used immediately after sterilization, these should be stored using appropriately sealed packaging and the established maximum hold time should be followed. Where justified, components that have been packaged with multiple sterile packaging layers need not be stored in a cleanroom if the integrity and configuration of the sterile pack allows the items to be readily disinfected during transfer by operators into grade A (for example, by the use of multiple sterile coverings that can be removed at each transfer from lower to higher grade). Where protection is achieved by containment in sealed packaging, this packaging process should be undertaken prior to sterilization.
- 8.47 Where materials, equipment, components and ancillary items are sterilized in sealed packaging and then transferred into grade A, this should be done using appropriate, validated methods (for example, airlocks or pass-through hatches) with accompanying disinfection of the exterior of the sealed packaging. The use of rapid transfer port technology should also be considered. These methods should be demonstrated to effectively control the potential risk of contamination of the grade A and B areas and, likewise, the disinfection procedure should be demonstrated to be effective in reducing any contamination on the packaging to acceptable levels for entry of the item into the grade A and B areas.
- 8.48 Where materials, equipment, components and ancillary items are sterilized in sealed packaging or containers, the packaging should be qualified for minimizing the risk of particulate, microbial, endotoxin/pyrogen or chemical contamination, and for compatibility with the selected sterilization method. The packaging sealing process should be validated. The validation should consider the integrity of the sterile protective barrier system, the maximum hold time before sterilization and the maximum shelf-life assigned to the sterilized items. The integrity of the sterile protective barrier system for each of the sterilized items should be checked prior to use.
- 8.49 For materials, equipment, components and ancillary items that are not a direct or indirect product contact part and are necessary for aseptic processing but cannot be sterilized, an effective and validated disinfection and transfer process should be in place. These items, once disinfected, should be protected to prevent recontamination. These items, and others representing potential routes of contamination, should be included in the environmental monitoring programme.

Sterilization by heat

- 8.50 Each heat sterilization cycle should be recorded either electronically or by hard copy, using equipment with suitable accuracy and precision. The system should have safeguards or redundancy in its control and monitoring instrumentation to detect a cycle not conforming to the validated cycle parameter requirements and abort or fail this cycle (for example, by the use of duplex or double probes connected to independent control and monitoring systems).
- 8.51 The position of the temperature probes used for controlling and recording should be determined during the validation and selected based on system design and in order to correctly record and represent routine cycle conditions. Validation studies should be designed to demonstrate the suitability of system control and recording probe locations, and should include the verification of the function and location of these probes by the use of an independent monitoring probe located at the same position during validation.
- 8.52 The whole of the load should reach the required temperature before measurement of the sterilizing time period starts. For sterilization cycles controlled by using a reference probe within the load, specific consideration should be given to ensuring that the load probe temperature is controlled within a defined temperature range prior to cycle commencement.
- 8.53 After completion of the high-temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling liquid or gas that comes into contact with the product or sterilized material should be sterilized.
- 8.54 In those cases where parametric release has been authorized, a robust system should be applied to the product life cycle validation and the routine monitoring of the manufacturing process. This system should be periodically reviewed.

Moist heat sterilization

- 8.55 Moist heat sterilization can be achieved using steam (direct or indirect contact), but also includes other systems such as superheated water systems (cascade or immersion cycles) that could be used for containers that may be damaged by other cycle designs (such as BFS containers or plastic bags).
- 8.56 The items to be sterilized, other than products in sealed containers, should be dry and packaged in a protective barrier system that allows removal of air and penetration of steam and prevents recontamination after sterilization. All loaded items should be dry upon removal from the sterilizer. Load dryness should be confirmed by visual inspection as a part of the sterilization process acceptance.

- 8.57 For porous cycles (hard goods), time, temperature and pressure should be used to monitor the process and should be recorded. Each sterilized item should be inspected for damage, packaging material integrity and moisture upon removal from the autoclave. Any item found not to be fit for purpose should be removed from the manufacturing area and an investigation performed.
- 8.58 For autoclaves capable of performing prevacuum sterilization cycles, the temperature should be recorded at the chamber drain throughout the sterilization period. Load probes may also be used where appropriate but the controlling system should remain related to the load validation. For steam-in-place systems, the temperature should be recorded at appropriate condensate drain locations throughout the sterilization period.
- 8.59 Validation of porous cycles should include a calculation of equilibration time, exposure time, correlation of pressure and temperature, and the minimum/maximum temperature range during exposure. Validation of fluid cycles should include temperature, time and F₀. Critical processing parameters should be subject to defined limits (including appropriate tolerances) and be confirmed as part of the sterilization validation and routine cycle acceptance criteria.
- 8.60 Leak tests on the sterilizer should be carried out periodically (normally weekly) when a vacuum phase is part of the cycle or the system is returned, post-sterilization, to a pressure lower than the environment surrounding the sterilizer.
- 8.61 There should be adequate assurance of air removal prior to and during sterilization when the sterilization process includes air purging (for example, porous autoclave loads, lyophilizer chambers). For autoclaves, this should include an air removal test cycle (normally performed on a daily basis) or the use of an air detector system. Loads to be sterilized should be designed to support effective air removal and be free draining to prevent the build-up of condensate.
- 8.62 Distortion and damage of non-rigid containers that are terminally sterilized, such as containers produced by BFS or FFS technologies, should be prevented by appropriate cycle design and control (for instance, setting correct pressure, heating and cooling rates and loading patterns).
- 8.63 Where steam-in-place systems are used for sterilization (for example, for fixed pipework, vessels and lyophilizer chambers), the system should be appropriately designed and validated to ensure that all parts of the system are subjected to the required treatment. The system should be monitored for temperature, pressure and time at appropriate locations during routine use to ensure all areas are effectively and reproducibly sterilized. These locations should be demonstrated as being representative of, and correlated with, the slowest to heat locations during

initial and routine validation. Once a system has been sterilized by steam-in-place it should remain integral and, where operations require, be maintained under positive pressure or otherwise equipped with a sterilizing vent filter prior to use.

- 8.64 In fluid load cycles where superheated water is used as the heat transfer medium, the heated water should consistently reach all of the required contact points. Initial qualification studies should include temperature mapping of the entire load. There should be routine checks on the equipment to ensure that nozzles (where the water is introduced) are not blocked and drains remain free from debris.
- 8.65 Validation of the sterilization of fluid loads in a superheated water autoclave should include temperature mapping of the entire load and heat penetration and reproducibility studies. All parts of the load should heat up uniformly and achieve the desired temperature for the specified time. Routine temperature monitoring probes should be correlated to the worst-case positions identified during the qualification process.

Dry heat sterilization

- 8.66 Dry heat sterilization utilizes high temperatures of air or gas to sterilize a product or article. Dry heat sterilization is of particular use in the thermal removal of difficult-to-eliminate thermally robust contaminants such as endotoxin/pyrogen and is often used in the preparation of components for aseptic filling. The combination of time and temperature to which product, components or equipment are exposed should produce an adequate and reproducible level of lethality and endotoxin/pyrogen inactivation or removal when operated routinely within the established limits. The process may be operated in an oven or in a continuous tunnel process (for example, for sterilization and depyrogenation of glass containers).
- 8.67 Dry heat sterilization or depyrogenation tunnels should be configured to ensure that airflow protects the integrity and performance of the grade A sterilizing zone by maintaining appropriate pressure differentials and airflow through the tunnel. Air pressure difference profiles should be established and monitored. Departures from established limits should be investigated, where appropriate. The impact of any airflow change should be assessed to ensure the heating profile is maintained. All air supplied to the tunnel should pass through at least a HEPA filter and periodic tests (at least every six months) should be performed to demonstrate air filter integrity. Any tunnel parts that come into contact with sterilized components should be appropriately sterilized or disinfected. Critical process parameters that should be considered during validation or routine processing should include:

- i. belt speed and dwell time within the sterilizing zone;
- ii. minimum and maximum temperatures;

- iii. heat penetration of the material or article;
 - iv. heat distribution and uniformity;
 - v. airflows determined by air pressure differential profiles correlated with the heat distribution and penetration studies.
- 8.68 When a thermal process is used as part of the depyrogenation process for any component or product contact equipment or material, validation studies should be performed to demonstrate that the process provides a suitable F_h value and results in a minimum 3 log₁₀ reduction in endotoxin concentration. When this is attained, there is no additional requirement to demonstrate sterilization in these cases.
- 8.69 Containers spiked with endotoxin should be used during validation and should be carefully managed with a full reconciliation performed. Containers should be representative of the materials normally processed (in respect to composition of the packaging materials, porosity, dimensions and nominal volume). Endotoxin quantification and recovery efficiency should also be demonstrated.
- 8.70 Dry heat ovens are typically employed to sterilize or depyrogenate primary packaging components, starting materials or active substances but may be used for other processes. They should be maintained at a positive pressure relative to lower-grade clean areas throughout the sterilization and post-sterilization hold process unless the integrity of the packaging is maintained. All air entering the oven should pass through a HEPA filter. Critical process parameters that should be considered in qualification or routine processing should include:
- i. temperature;
 - ii. exposure period or time;
 - iii. chamber pressure (for maintenance of overpressure);
 - iv. air speed;
 - v. air quality within the oven;
 - vi. heat penetration of material or article (slow-to-heat spots);
 - vii. heat distribution and uniformity;
 - viii. load pattern and configuration of articles to be sterilized or depyrogenated, including minimum and maximum loads.

Sterilization by radiation

- 8.71 Sterilization by radiation is used mainly for the sterilization of heat-sensitive materials and products. Ultraviolet irradiation is not an acceptable method of sterilization.

8.72 Validation procedures should ensure that the effects of variation in the density of the product and packages are considered.

Sterilization with ethylene oxide

8.73 This method should only be used when no other method is practicable. During process validation, it should be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing result in the reduction of any residual ethylene oxide gas and reaction products to defined acceptable limits for the given product or material.

8.74 Direct contact between gas and microbial cells is essential. Precautions should be taken to avoid the presence of organisms likely to be enclosed in material, such as crystals or dried protein. The nature, porosity and quantity of packaging materials can significantly affect the process.

8.75 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process. Where steam is used to condition the load for sterilization, it should be of an appropriate quality. The time required for this should be balanced against the opposing need to minimize the time before sterilization.

8.76 Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test units distributed throughout the load at defined locations that have been shown to be worst-case locations during validation.

8.77 Critical process parameters that should be considered as part of the sterilization process validation and routine monitoring include:

- i. ethylene oxide gas concentration
- ii. pressure
- iii. the amount of ethylene oxide gas used
- iv. relative humidity
- v. temperature
- vi. exposure time.

8.78 After sterilization, the load should be aerated to allow ethylene oxide gas or its reaction products to desorb from the packaged product to predetermined levels. Aeration can occur within a sterilizer chamber or in a separate aeration chamber or aeration room. The aeration phase should be validated as part of the overall ethylene oxide sterilization process validation.

Sterilization by filtration of products that cannot be sterilized in their final container

- 8.79 If the product cannot be sterilized in its final container, solutions or liquids should be sterilized by filtration through a sterile sterilizing grade filter (with a nominal pore size of a maximum of 0.22 µm that has been appropriately validated to obtain a sterile filtrate) and subsequently aseptically filled into a previously sterilized container. The selection of the filter used should ensure that it is compatible with the product and is as described in the marketing authorization (refer to paragraph 8.135).
- 8.80 Suitable bioburden reduction prefilters or sterilizing grade filters may be used at multiple points during the manufacturing process to ensure a low and controlled bioburden of the liquid prior to the final sterilizing filter. Due to the potential additional risks of a sterile filtration process, as compared with other sterilization processes, an additional filtration through a sterile sterilizing grade filter, as close to the point of fill as possible, should be considered as part of an overall CCS.
- 8.81 The selection of components for the filtration system and their interconnection and arrangement within the filtration system, including prefilters, should be based on the critical quality attributes of the product, justified and documented. The filtration system should minimize the generation of fibres and particles and should not cause or contribute to unacceptable levels of impurities or possess characteristics that otherwise alter the quality and efficacy of the product. Similarly, the filter characteristics should be compatible with the fluid and not be adversely affected by the product to be filtered. Adsorption of product components and extraction or leaching of filter components should be evaluated (refer to paragraph 8.135).
- 8.82 The filtration system should be designed to:
- i. allow operation within validated process parameters;
 - ii. maintain the sterility of the filtrate;
 - iii. minimize the number of aseptic connections required between the final sterilizing grade filter and the final filling of the product;
 - iv. allow cleaning procedures to be conducted as necessary;
 - v. allow sterilization procedures, including sterilization in place, to be conducted as necessary;
 - vi. permit in-place integrity testing of the 0.22 µm final sterilizing grade filter, preferably as a closed system, both prior to and following filtration as necessary; in-place integrity testing methods should be selected to avoid any adverse impact on the quality of the product.

- 8.83 Sterile filtration of liquids should be validated in accordance with relevant pharmacopoeial requirements. Validation can be grouped by different strengths or variations of a product but should be based on risk (for example, product and conditions). The rationale for grouping should be justified and documented.
- 8.84 During filter validation, wherever possible, the product to be filtered should be used for bacterial retention testing of the sterilizing grade filter. Where the product to be filtered is not suitable for use in bacterial retention testing, a suitable surrogate product should be selected and should be justified for use in the test. The challenge organism used in the bacterial retention test should be justified.
- 8.85 Filtration parameters that should be considered and established during validation should include:
- i. The wetting fluid used for filter integrity testing should be based on the filter manufacturer's recommendation or the fluid to be filtered. The appropriate integrity test value specification should be established.
 - ii. If the system is flushed or integrity tested in situ with a fluid other than the product, the appropriate actions should be taken to avoid any deleterious effect on product quality.
- Filtration process conditions to be considered include:
- i. fluid prefiltration holding time and effect on bioburden;
 - ii. filter conditioning, with fluid if necessary;
 - iii. maximum filtration time or total time filter is in contact with the fluid;
 - iv. maximum operating pressure;
 - v. flow rate;
 - vi. maximum filtration volume;
 - vii. temperature;
 - viii. the time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter.
- 8.86 Routine process controls should be implemented to ensure adherence to validated filtration parameters. The results of critical process parameters should be included in the batch record, including the minimum time taken to filter a known volume of bulk solution and pressure difference across the filter. Any significant difference from critical parameters during manufacturing should be documented and investigated.
- 8.87 The integrity of the sterilized filter assembly should be verified by integrity testing before use (pre-use post-sterilization integrity test or PUPSIT) to check

for damage and loss of integrity caused by the filter preparation prior to use. A sterilizing grade filter that is used to sterilize a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing. The integrity test process should be validated and test results should correlate to the microbial retention capability of the filter established during validation. Examples of tests that are used include bubble point, diffusive flow, water intrusion or pressure hold test. It is recognized that PUPSIT may not always be possible after sterilization due to process constraints (such as the filtration of very small volumes of solution). In these cases, an alternative approach may be taken provided that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of a non-integral filtration system. Points to consider in such a risk assessment should include:

- i. in-depth knowledge and control of the filter sterilization process to ensure that the potential for damage to the filter is minimized;
- ii. in-depth knowledge and control of the supply chain to include:
 - contract sterilization facilities
 - defined transport mechanisms
 - packaging of the sterilized filter to prevent damage to the filter during transportation and storage;
- iii. in-depth process knowledge, such as:
 - the specific product type, including particle burden and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test;
 - prefiltration and processing steps, prior to the final sterilizing grade filter, which would remove particle burden and clarify the product prior to the sterile filtration.

8.88 The integrity of critical sterile gas and air vent filters (that are directly linked to the sterility of the product) should be verified by testing after use, with the filter remaining in the filter assembly or housing.

8.89 The integrity of non-critical air or gas vent filters should be confirmed and recorded at appropriate intervals. Where gas filters are in place for extended periods, integrity testing should be carried out at installation and prior to replacement. The maximum duration of use should be specified and monitored based on risk (for example, considering the maximum number of uses and heat treatment or sterilization cycles permitted, as applicable).

- 8.90 For gas filtration, unintended moistening or wetting of the filter or filter equipment should be avoided.
- 8.91 If the sterilizing filtration process has been validated as a system consisting of multiple filters to achieve the sterility for a given fluid, the filtration system is considered to be a single sterilizing unit and all filters within the system should satisfactorily pass integrity testing after use.
- 8.92 In a redundant filtration system (where a second redundant sterilizing grade filter is present as a backup but the sterilizing process is validated as only requiring one filter), a post-use integrity test of the primary sterilizing grade filter should be performed and, if it is demonstrated to be integral, then a post-use integrity test of the redundant (backup) filter is not necessary. However, in the event of a failure of the post-use integrity test on the primary filter, a post-use integrity test on the secondary (redundant) filter should be performed, in conjunction with an investigation and risk assessment to determine the reason for the primary filter test failure.
- 8.93 Bioburden samples should be taken from the bulk product and immediately prior to the final sterile filtration. In cases where a redundant filtration set-up is used, it should be taken prior to the first filter. Systems for taking samples should be designed so as not to introduce contamination.
- 8.94 Liquid sterilizing grade filters should be discarded after the processing of a single batch and the same filter should not be used continuously for more than one working day unless such use has been validated.
- 8.95 Where campaign manufacture of a product has been appropriately justified in the CCS and validated, the filter user should:
- i. assess and document the risks associated with the duration of filter use for the sterile filtration process for a given fluid;
 - ii. conduct and document effective validation and qualification studies to demonstrate that the duration of filter use for a given sterile filtration process and for a given fluid does not compromise the performance of the final sterilizing grade filter or filtrate quality;
 - iii. document the maximum validated duration of use for the filter and implement controls to ensure that filters are not used beyond the validated maximum duration, and maintain records of these controls;
 - iv. implement controls to ensure that filters contaminated with fluid or cleaning agent residues, or considered defective in any other way, are removed from use.

Form-fill-seal (FFS)

- 8.96 The conditions for FFS machines used for terminally sterilized products should comply with the environmental requirements of paragraphs 8.3 and 8.4 of this guideline. The conditions for FFS machines used in aseptic manufacture should comply with the environmental requirements of paragraph 8.10 of this guideline.
- 8.97 Contamination of the packaging films used in the FFS process should be minimized by appropriate controls during component production, supply and handling. Due to the criticality of packaging films, procedures should be implemented to ensure that the films supplied meet defined specifications and are of the appropriate quality, including material thickness and strength, microbial and particulate contamination, integrity and artwork, as relevant. The sampling frequency, the bioburden and, where applicable, endotoxin/pyrogen levels of packaging films and associated components should be defined and controlled within the PQS and considered in the CCS.
- 8.98 Particular attention should be given to understanding and assessing the operation of the equipment, including set-up, filling, sealing and cutting processes, so that critical process parameters are understood, validated, controlled and monitored appropriately.
- 8.99 Any product contact gases (such as those used to inflate the container or used as a product overlay) should be appropriately filtered, as close to the point of use as possible. The quality of gases used and the effectiveness of gas filtration systems should be verified periodically in accordance with paragraphs 6.18 and 6.19.
- 8.100 The controls identified during qualification of FFS should be in alignment with the CCS. Aspects to be considered include:
- i. determination of the boundaries of the critical zone;
 - ii. environmental control and monitoring of both the machine and the background in which it is placed;
 - iii. personnel gowning requirements;
 - iv. integrity testing of the product filling lines and filtration systems, as relevant;
 - v. duration of the batch or filling campaign;
 - vi. control of packaging films, including any requirements for film decontamination or sterilization;
 - vii. cleaning in place and sterilization in place of equipment, as necessary;
 - viii. machine operation, settings and alarm management, as relevant.

- 8.101 Critical process parameters for FFS should be determined during equipment qualification and should include:
- i. settings for uniform package dimensions and cutting in accordance with validated parameters;
 - ii. setting, maintenance and monitoring of validated forming temperatures (including preheating and cooling), forming times and pressures, as relevant;
 - iii. setting, maintenance and monitoring of validated sealing temperatures, sealing temperature uniformity across the seal, sealing times and pressures, as relevant;
 - iv. environmental and product temperature;
 - v. batch-specific testing of package seal strength and uniformity;
 - vi. settings for correct filling volumes, speeds and uniformity;
 - vii. settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity is not compromised;
 - viii. methods and parameters for integrity testing of filled containers (refer to paragraph 8.22).
- 8.102 The appropriate procedures for the verification, monitoring and recording of FFS critical process parameters and equipment operation should be applied during production.
- 8.103 Operational procedures should describe how forming and sealing issues are detected and rectified. Rejected units or sealing issues should be recorded and investigated.
- 8.104 The appropriate maintenance procedures should be established based on risk, and should include maintenance and inspection plans for tooling critical to the effectiveness of unit sealing. Any issues identified that indicate a potential product quality concern should be documented and investigated.

Blow-fill-seal (BFS)

- 8.105 BFS equipment used for the manufacture of products that are terminally sterilized should be installed in at least a grade D environment. The conditions at the point of fill should comply with the environmental requirements of paragraphs 8.3 and 8.4.
- 8.106 BFS used for aseptic processing:
- i. For shuttle type equipment used for aseptic filling, the parison is open to the environment. Therefore the areas where parison extrusion, blow

moulding and sealing take place should meet grade A conditions at the critical zones. The filling environment should be designed and maintained to meet grade A conditions for viable and total particle limits both at rest and when in operation.

- ii. For rotary-type equipment used for aseptic filling, the parison is generally closed to the environment once formed. The filling environment within the parison should be designed and maintained to meet grade A conditions for viable and total particle limits both at rest and when in operation.
 - iii. The equipment should be installed in at least a grade C environment, provided that grade A/B clothing is used. The microbiological monitoring of operators wearing grade A/B clothing in a grade C area should be performed in accordance with risk management principles. The limits and monitoring frequencies should be applied with consideration of the activities performed by these operators.
- 8.107 Due to the generation of particles from polymer extrusion, cutting during operation, and the restrictive size of critical filling zones of BFS equipment, in operation monitoring of total particle for BFS equipment is not expected. However, data should be available to demonstrate that the design of the equipment ensures that critical zones of the filling process environment would meet grade A conditions in operation.
- 8.108 Viable environmental monitoring of BFS processes should be risk based and designed in accordance with section 9 of this guideline. In operation viable monitoring should be undertaken for the full duration of critical processing, including equipment assembly. For rotary-type BFS equipment, it is acknowledged that monitoring of the critical filling zone may not be possible.
- 8.109 The environmental control and monitoring programme should take into consideration the moving parts and complex airflow paths generated by the BFS process and the effect of the high heat outputs of the process (for example, through the use of airflow visualization studies or other equivalent studies). Environmental monitoring programmes should also consider factors such as air filter configuration, air filter integrity, cooling system integrity (refer to paragraph 6.21), equipment design and qualification.
- 8.110 Air or other gases that make contact with critical surfaces of the container during extrusion, formation or sealing of the moulded container should undergo appropriate filtration. The quality of gas used and the effectiveness of gas filtration systems should be verified periodically in accordance with paragraphs 6.18 and 6.19.

- 8.111 Particulate and microbial contamination of the polymer granulate should be prevented by the appropriate design, control and maintenance of the polymer granulate storage, sampling and distribution systems.
- 8.112 The capability of the extrusion system to provide appropriate sterility assurance for the moulded container should be understood and validated. The sampling frequency, the bioburden and, where applicable, endotoxin/pyrogen levels of the raw polymer should be defined and controlled within the PQS and considered in the CCS.
- 8.113 Interventions requiring cessation of filling or extrusion, moulding and sealing and, where required, resterilization of the filling machine should be clearly defined and described in the filling procedure, and included in the APS as relevant (refer to paragraphs 9.34, 9.35 and 9.36).
- 8.114 The controls identified during qualification of BFS should be in alignment with the site's CCS. Aspects to be considered include:
- i. determination of the boundaries of the critical zone;
 - ii. environmental control and monitoring of both the machine and the background in which it is placed;
 - iii. personnel gowning requirements;
 - iv. integrity testing of the product filling lines and filtration systems, as relevant;
 - v. duration of the batch or filling campaign;
 - vi. control of polymer granulate, including distribution systems and critical extrusion temperatures;
 - vii. cleaning in place and sterilization in place of equipment, as necessary;
 - viii. machine operation, settings and alarm management, as relevant.
- 8.115 Critical process parameters for BFS should be determined during equipment qualification and should include:
- i. cleaning in place and sterilization in place of product pipelines and filling needles (mandrels);
 - ii. setting, maintenance and monitoring of extrusion parameters, including temperature, speed and extruder throat settings for parison thickness;
 - iii. setting, maintenance and monitoring of mould temperatures, including rate of cooling where necessary for product stability;
 - iv. preparation and sterilization of ancillary components added to the moulded unit, such as bottle caps;

- v. environmental control, cleaning, sterilization and monitoring of the critical extrusion, transfer and filling areas, as relevant;
 - vi. batch-specific testing of package wall thickness at critical points of the container;
 - vii. settings for correct filling volumes, speeds and uniformity;
 - viii. settings for any additional printing (batch coding), embossing or debossing to ensure that unit integrity and quality are not compromised;
 - ix. methods and parameters for integrity testing of 100% of all filled containers (refer to paragraph 8.22);
 - x. settings for cutters or punches used to remove waste plastic surrounding filled units (flash removal).
- 8.116 The appropriate procedures for the verification, monitoring and recording of BFS critical process parameters and equipment operation should be applied during production.
- 8.117 Operational procedures should describe how blowing, forming and sealing issues are detected and rectified. Rejected units or sealing issues should be recorded and investigated.
- 8.118 Where the BFS process includes the addition of components to moulded containers (for example, addition of caps to large-volume parenteral bottles), these components should be appropriately decontaminated and added to the process using a clean, controlled process.
- i. For aseptic processes, the addition of components should be performed under grade A conditions to ensure the sterility of critical surfaces using presterilized components.
 - ii. For terminally sterilized products, the validation of terminal sterilization processes should ensure the sterility of all critical product pathways between the component and moulded container, including areas that are not wetted during sterilization.
 - iii. Testing procedures should be established and validated to ensure the effective sealing of components and moulded containers.
- 8.119 The appropriate maintenance procedures should be established based on risk, and should include maintenance and inspection plans for items critical to unit sealing, integrity and sterility.
- 8.120 The moulds used to form containers are considered critical equipment and any changes or modification to moulds should result in an assessment of finished

product container integrity and, where the assessment indicates, should be supported by validation. Any issues identified that indicate a potential product quality concern should be documented and investigated.

Lyophilization

- 8.121 Lyophilization is a critical process step and all activities that can affect the sterility of the product or material need to be regarded as extensions of the aseptic processing of the sterilized product. The lyophilization equipment and its processes should be designed to ensure that product or material sterility is maintained during lyophilization by preventing microbial and particle contamination between the filling of products for lyophilization and completion of the lyophilization process. All control measures in place should be determined by the site's CCS.
- 8.122 The sterilization of the lyophilizer and associated equipment (such as trays and vial support rings) should be validated, and the holding time between the sterilization cycle and use appropriately challenged during APS (refer to paragraph 9.33). Resterilization should be performed following maintenance or cleaning. Sterilized lyophilizers and associated equipment should be protected from contamination after sterilization.
- 8.123 Lyophilizers and associated product transfer and loading or unloading areas should be designed to minimize operator intervention as far as possible. The frequency of lyophilizer sterilization should be determined based on the design and risks related to system contamination during use. Lyophilizers that are manually loaded or unloaded with no barrier technology separation should be sterilized before each load. For lyophilizers loaded and unloaded by automated systems or protected by closed barrier systems, the frequency of sterilization should be justified and documented as part of the CCS.
- 8.124 The integrity of the lyophilizer should be maintained following sterilization and during lyophilization. The filter used to maintain lyophilizer integrity should be sterilized before each use of the system and its integrity testing results should be part of the batch certification and release. The frequency of vacuum and leak integrity testing of the chamber should be documented and the maximum permitted leakage of air into the lyophilizer should be specified and checked at the start of every cycle.
- 8.125 Lyophilization trays should be checked regularly to ensure that they are not misshapen or damaged.
- 8.126 Points to consider for the design of loading (and unloading, where the lyophilized material is still unsealed and exposed) include:

- i. Loading patterns within the lyophilizer are specified and documented.
- ii. The transfer of partially closed containers to a lyophilizer are undertaken under grade A conditions at all times and handled in a manner designed to minimize direct operator intervention. Technologies such as conveyor systems or portable transfer systems (for example, clean air transfer carts, portable unidirectional airflow workstations) should be used to ensure that the cleanliness of the system used to transfer the partially closed containers is maintained. Alternatively, where supported by validation, trays closed in a grade A area and not reopened whilst in the grade B area may be used to protect partially stoppered vials (such as appropriately closed boxes).
- iii. Airflow patterns are not to be adversely affected by transport devices and venting of the loading zone.
- iv. Unsealed containers (such as partially stoppered vials) are maintained under grade A conditions and should normally be separated from operators by physical barrier technology or any other appropriate measures.
- v. With regard to opening the lyophilizer chamber after incomplete closure or partial stoppering of product or material, product removed from the lyophilizer should remain under grade A conditions during subsequent handling.
- vi. Utensils used during loading and unloading of the lyophilizer (such as trays, bags, placing devices and tweezers) should be kept sterile.

Closed systems

- 8.127 The use of closed systems can reduce the risk of microbial, particle and chemical contamination from the adjacent environment. Closed systems should always be designed to reduce the need for manual manipulation and the associated risks.
- 8.128 It is critical to ensure the sterility of all product contact surfaces of closed systems used for aseptic processing. The design and selection of any closed system used for aseptic processing should ensure that sterility is achieved and maintained. The connection of sterile equipment (such as tubing or pipework) to the sterilized product pathway after the final sterilizing grade filter should be designed to be connected aseptically (for example, by intrinsic sterile connection devices).
- 8.129 The appropriate measures should be in place to ensure the integrity of components used in aseptic connections. The means by which this is achieved should be determined and captured in the CCS. The appropriate system integrity tests should be considered when there is a risk of compromising product sterility. The

supplier assessment should include the collation of data in relation to potential failure modes that may lead to a loss of system sterility.

- 8.130 The background environment in which closed systems are located should be based on their design and the processes undertaken. For aseptic processing and where there are any risks that system integrity may be compromised, the system should be located in grade A. If the system can be shown to remain integral at every usage (for example, via pressure testing and monitoring) then a lower-classified area may be used. Any transfer between classified areas should be thoroughly assessed (refer to paragraph 4.10). If the closed system is opened (for example, for maintenance of a bulk manufacturing line), then this should be performed in a classified area appropriate to the materials (for example, grade C for terminal sterilization processes or grade A for aseptic processing) or be subject to further cleaning and disinfection (and sterilization in the case of aseptic processes).

Single-use systems

- 8.131 Single-use systems (SUS) are those technologies used in manufacture of sterile products that are used as an alternative to reusable equipment. They can be individual components or made up of multiple components such as bags, filters, tubing, connectors, valves, storage bottles and sensors. SUS should be designed to reduce the need for manipulation and complexity of manual interventions.
- 8.132 There are some specific risks associated with SUS that should be assessed as part of the CCS. These risks include:
- i. the interaction between the product and product contact surface (such as adsorption, or leachables and extractables);
 - ii. the fragile nature of the system compared with fixed reusable systems;
 - iii. the increase in the number and complexity of manual operations (including inspection and handling of the system) and connections made;
 - iv. the complexity of the assembly;
 - v. the performance of the pre- and post-use integrity testing for sterilizing grade filters (refer to paragraph 8.87);
 - vi. the risk of holes and leakage;
 - vii. the potential for compromising the system at the point of opening the outer packaging;
 - viii. the risk of particle contamination.
- 8.133 Sterilization processes for SUS should be validated and shown to have no adverse impact on system performance.

- 8.134 The assessment of suppliers of disposable systems, including sterilization, is critical to the selection and use of these systems. For sterile SUS, verification of sterility assurance should be performed as part of the supplier qualification and evidence of sterilization of each unit should be checked on receipt.
- 8.135 The adsorption and reactivity of the product with product contact surfaces should be evaluated under process conditions.
- 8.136 The extractable and leachable profiles of the SUS and any impact on the quality of the product, especially where the system is made from polymer-based materials, should be evaluated. An assessment should be carried out for each component to evaluate the applicability of the extractable profile data. For components considered to be at high risk from leachables, including those that may absorb processed materials or those with extended material contact times, an assessment of leachable profile studies, including safety concerns, should be taken into consideration. If applying simulated processing conditions, these should accurately reflect the actual processing conditions and be based on a scientific rationale.
- 8.137 SUS should be designed to maintain integrity throughout processing under the intended operational conditions. Attention to the structural integrity of the single-use components is necessary where these may be exposed to more extreme conditions (such as freezing and thawing processes) during either routine processing or transportation. This should include verification that intrinsic sterile connection devices (both heat sealed and mechanically sealed) remain integral under these conditions.
- 8.138 Acceptance criteria should be established and implemented for SUS corresponding to the risks or criticality of the product and its processes. Upon receipt, each piece of an SUS should be checked to ensure that they have been manufactured, supplied and delivered in accordance with the approved specification. A visual inspection of the outer packaging (including appearance of exterior carton and product pouches) and label printing and review of attached documents (such as a certificate of conformance and proof of sterilization) should be carried out and documented prior to use.
- 8.139 The critical manual handling operations of SUS, such as assembly and connections, should be subject to the appropriate controls and verified during APS.

9. Environmental and process monitoring

General

- 9.1 The site's environmental and process monitoring programme forms part of the overall CCS and is used to monitor the controls designed to minimize the risk of microbial and particle contamination. It should be noted that the reliability of each of the elements of the monitoring system (viable, non-viable and APS) when taken in isolation is limited and should not be considered individually to be an indicator of asepsis. When considered together, the results help confirm the reliability of the design, validation and operation of the system that they are monitoring.
- 9.2 This programme typically comprises the following elements:
- i. environmental monitoring – total particle
 - ii. environmental and personnel monitoring – viable particle
 - iii. temperature, relative humidity and other specific characteristics
 - iv. APS (aseptically manufactured product only).
- 9.3 The information from these systems should be used for routine batch certification and release and for periodic assessment during process review or investigation. This applies for both terminal sterilization and aseptic processes; however, the criticality of the impact may differ depending upon the product and process type.

Environmental and process monitoring

- 9.4 An environmental monitoring programme should be established and documented. The purpose of the environmental monitoring programme is to:
- i. provide assurance that cleanrooms and clean air equipment continue to provide an environment of appropriate air cleanliness, in accordance with design and regulatory requirements;
 - ii. effectively detect excursions from environmental limits triggering investigation and assessment of risk to product quality.

Risk assessments should be performed in order to establish this comprehensive environmental monitoring programme, such as sampling locations, frequency of monitoring, monitoring methods and incubation conditions (such as time, temperature, and aerobic or anaerobic conditions).

These risk assessments should be conducted based on detailed knowledge of the process inputs and final product, the facility, equipment, the criticality of specific processes and steps, the operations involved, routine monitoring data, monitoring data obtained during qualification and knowledge of typical microbial flora isolated from the environment.

The risk assessment should include the determination of critical monitoring locations – those locations where the presence of microorganisms during processing may have an impact upon product quality (for example, grade A aseptic processing areas and grade B areas that directly interface with grade A areas). Consideration of other information, such as air visualization studies, should also be included. These risk assessments should be reviewed regularly in order to confirm the effectiveness of the site's environmental monitoring programme. The monitoring programme should be considered in the overall context of the trend analysis and the CCS for the site.

- 9.5 The routine monitoring of cleanrooms, clean air equipment and personnel should be performed in operation throughout all critical stages of processing, including equipment set-up.
- 9.6 Other characteristics, such as temperature and relative humidity, should be controlled within ranges that align with product, processing and personnel requirements and support maintenance of defined cleanliness standards (for example, grades A or B).
- 9.7 The monitoring of grade A should demonstrate the maintenance of aseptic processing conditions during critical operations. Monitoring should be performed at locations posing the highest risk of contamination of the sterile equipment surfaces, containers, closures and product. The selection of monitoring locations and the orientation and positioning of sampling devices should be justified and appropriate to obtain reliable data from the critical zones.
- 9.8 Sampling methods should not pose a risk of contamination of the manufacturing operations.
- 9.9 The appropriate alert limits and action limits should be set for the results of viable and total particle monitoring. The maximum total particle action limits are described in Table 5 and the maximum viable particle action limits are described in Table 6. However, more stringent action limits may be applied based on data trending or the nature of the process, or as determined within the CCS. Both viable and total particle alert levels should be established based on results of cleanroom qualification tests and periodically reviewed based on ongoing trend data.
- 9.10 Alert limits for grade A (total particle only), grade B, grade C and grade D should be set such that adverse trends (for example, a number of events or individual events that indicate a deterioration of environmental control) are detected and addressed.
- 9.11 Monitoring procedures should define the approach to trending. Trends should include:

- i. increasing numbers of excursions from alert limits and action limits;
 - ii. consecutive excursions from alert limits;
 - iii. regular but isolated excursion from action limits that may have a common cause (for example, single excursions that always follow planned preventive maintenance);
 - iv. changes in microbial flora type and numbers and predominance of specific organisms, paying particular attention to organisms recovered that may indicate a loss of control or deterioration in cleanliness or organisms that may be difficult to control, such as spore-forming microorganisms and moulds.
- 9.12 The monitoring of grade C and D cleanrooms in operation should be performed based on data collected during qualification and routine data to allow effective trend analysis. The requirements of alert limits and action limits will depend on the nature of the operations carried out. Action limits may be more stringent than those listed in Tables.5 and.6 below.
- 9.13 If alert limits are exceeded, operating procedures should prescribe assessment and follow up, which should include consideration of an investigation or corrective actions to avoid any further deterioration of the environment. If action limits are exceeded, operating procedures should prescribe a root cause investigation, an assessment of the potential impact to product (including batches produced between the monitoring and reporting) and requirements for corrective and preventive action.

Environmental monitoring: total particle

- 9.14 A total particle monitoring programme should be established to obtain data for assessing potential contamination risks and to ensure the maintenance of the environment for sterile operations in a qualified state.
- 9.15 The limits for environmental monitoring of airborne particle concentration for each graded area are given in Table. 5.

Table. 5**Maximum permitted total particle concentration for monitoring**

Grade	Maximum limits for total particle ≥ 0.5 µm/m³		Maximum limits for total particle ≥ 5 µm/m³	
	At rest	In operation	At rest	In operation
A	3 520	3 520	29	29
B	3 520	352 000	29	2 930
C	352 000	3 520 000	2 930	29 300
D	3 520 000	Not predetermined ^a	29 300	Not predetermined ^a

^a For grade D, in operation limits are not predetermined. The manufacturer should establish in operation limits based on a risk assessment and on routine data, where applicable.

Note 1: The particle limits given in the table for the at rest state should be achieved after a short clean-up period defined during qualification (guidance value of less than 20 minutes) in an unmanned state, after the completion of operations (refer to paragraph 4.29).

Note 2: The occasional indication of macro particle counts, especially ≥ 5 µm, within grade A may be considered to be false counts due to electronic noise, stray light, coincidence loss, or other factor. However, consecutive or regular counting of low levels may be indicative of a possible contamination event and should be investigated. Such events may indicate early failure of the room air supply filtration system or equipment failure, or may be diagnostic of poor practices during machine set-up and routine operation.

9.16 For grade A, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly.

9.17 The grade A area should be monitored continuously (for particles ≥ 0.5 and ≥ 5 µm) and with a suitable sample flow rate (at least 28 litres per minute) so that all interventions, transient events and any system deterioration is captured. The system should frequently correlate each individual sample result with alert levels and action limits at such a frequency that any potential excursion can be identified and responded to in a timely manner. Alarms should be triggered if alert levels are exceeded. Procedures should define the actions to be taken in response to alarms, including the consideration of additional microbial monitoring.

9.18 It is recommended that a similar system be used for the grade B area, though the sampling frequency may be decreased. The grade B area should be monitored at such a frequency and with suitable sample size that the programme captures any increase in levels of contamination and system deterioration. If alert limits are exceeded, alarms should be triggered.

9.19 The selection of the monitoring system should take into account any risk presented by the materials used in the manufacturing operation (for example, those involving

live organisms, powdery products or radiopharmaceuticals) that may give rise to biological, chemical or radiation hazards.

- 9.20 In the case where contaminants are present due to the processes involved, and would potentially damage the particle counter or present a hazard (for example, live organisms, powdery products and radiation hazards), the frequency and strategy employed should be appropriate to assure the environmental classification both prior to and post exposure to the risk. An increase in viable particle monitoring should be considered to ensure comprehensive monitoring of the process. Additionally, monitoring should be performed during simulated operations. Such operations should be performed at appropriate intervals. The approach should be defined in the CCS.
- 9.21 The size of monitoring samples taken using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of cleanrooms and clean air equipment. Monitoring sample volumes should be justified.

Environmental and personnel monitoring: viable particle

- 9.22 Where aseptic operations are performed, microbial monitoring should be frequent using a combination of methods such as settle plates, volumetric air sampling, glove, gown and surface sampling (for example, using swabs and contact plates). The method of sampling used should be justified within the CCS and should be demonstrated not to have a detrimental impact on grade A and B airflow patterns. Cleanroom and equipment surfaces should be monitored at the end of an operation.
- 9.23 Viable particle monitoring should also be performed within the cleanrooms when normal manufacturing operations are not occurring (for example, post disinfection, prior to start of manufacturing, upon completion of the batch and after a shutdown period), and in associated rooms that have not been used in order to detect potential incidents of contamination that may affect the controls within the cleanrooms. In case of an incident, additional sample locations may be used as a verification of the effectiveness of a corrective action (such as cleaning and disinfection).
- 9.24 Continuous viable air monitoring in grade A (for example, air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and critical processing. A similar approach should be considered for grade B cleanrooms based on the risk of impact on the aseptic processing. The monitoring should be performed in such a way that all interventions, transient events and any system deterioration would be detected and captured to alert any risk caused.

- 9.25 A risk assessment should evaluate the locations, type and frequency of personnel monitoring based on the activities performed and the proximity to critical zones. Monitoring should include sampling of personnel at periodic intervals during the process. Sampling of personnel should be performed in such a way that it will not compromise the process. Particular consideration should be given to monitoring personnel following involvement in critical interventions (at a minimum gloves, but may require monitoring of areas of gown as applicable to the process) and on each exit from the grade B cleanroom (gloves and gown). Where the monitoring of gloves is performed after critical interventions, outer gloves should be replaced prior to continuation of activity. Where the monitoring of gowns is required after critical interventions, each gown should be replaced before further activity in the cleanroom.
- 9.26 Microbial monitoring of personnel in the grade A and B areas should be performed. Where operations are manual in nature (such as aseptic compounding or filling), the increased risk should lead to enhanced emphasis placed on microbial monitoring of gowns and justified within the CCS.
- 9.27 Where monitoring is routinely performed by manufacturing personnel, this should be subject to regular oversight by the quality unit (refer also to paragraph 8.19).
- 9.28 The adoption of suitable alternative monitoring systems, such as rapid methods, should be considered by manufacturers in order to expedite the detection of microbiological contamination issues and to reduce the risk to product. These rapid and automated microbial monitoring methods may be adopted after validation has demonstrated their equivalency or superiority to the established methods.
- 9.29 Sampling methods and equipment used should be fully understood and procedures should be in place for the correct operation and interpretation of results obtained. Supporting data for the recovery efficiency of the sampling methods chosen should be available.
- 9.30 Action limits for viable particle contamination are shown in Table. 6.

Table. 6**Maximum action limits for viable particle contamination**

Grade	Air sample CFU/m ³	Settle plates (diam. 90 mm) CFU/4 hours ^a	Contact plates (diam. 55 mm) CFU/plate ^b	Glove print, incl. 5 fingers on both hands CFU/glove
A			No growth ^c	
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

CFU = colony-forming unit.

^a Settle plates should be exposed in grade A and B areas for the duration of operations (including equipment set-up) and changed as required after a maximum of 4 hours (exposure time should be based on validation including recovery studies, and should not have any negative effect on the suitability of the media used). For grade C and D areas, exposure time (with a maximum of 4 hours) and frequency should be based on quality risk management. Individual settle plates may be exposed for less than 4 hours.

^b Contact plate limits apply to equipment, room and gown surfaces within the grade A and B areas. Routine gown monitoring is not normally required for grade C and D areas, depending on their use.

^c It should be noted that for grade A, any growth should result in an investigation.

Note 1: It should be noted that the types of monitoring methods listed in the table above are examples and other methods can be used provided they meet the intent of providing information across the whole of the critical process where product may be contaminated (for example, aseptic line set-up, aseptic processing, filling and lyophilizer loading).

Note 2: Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and, where possible, correlate them to CFU.

9.31 Microorganisms detected in the grade A and grade B areas should be identified to species level and the potential impact of such microorganisms on product quality (for each batch implicated) and overall state of control should be evaluated. Consideration should also be given to the identification of microorganisms detected in grade C and D areas (for example, where action limits or alert levels are exceeded) or following the isolation of organisms that may indicate a loss of control or deterioration in cleanliness or that may be difficult to control, such as spore-forming microorganisms and moulds, and at a sufficient frequency to maintain a current understanding of the typical flora of these areas.

Aseptic process simulation

9.32 Periodic verification of the effectiveness of the controls in place for aseptic processing should include an aseptic process simulation (APS) (also known as media fill) using a sterile nutrient medium or surrogate in place of the product. The APS should not

be considered as the primary means to validate the aseptic process or aspects of the aseptic process. The effectiveness of the aseptic process should be determined through process design, adherence to the PQS and process controls, training, and evaluation of monitoring data. Selection of an appropriate nutrient medium or surrogate should be made based on the ability of the medium or surrogate to imitate physical product characteristics assessed to pose a risk to product sterility during the aseptic process. Where processing stages may indirectly impact the viability of any introduced microbial contamination (for example, aseptically produced semi-solids, powders, solid materials, microspheres, liposomes and other formulations where product is cooled or heated or lyophilized), alternative procedures that represent the operations as closely as possible should be developed. Where surrogate materials, such as buffers, are used in parts of the APS, the surrogate material should not inhibit the growth of any potential contamination.

9.33 The APS should imitate as closely as possible the routine aseptic manufacturing process and include all the critical manufacturing steps, specifically:

- i. The APS should cover all aseptic operations performed subsequent to the sterilization and decontamination cycles of materials utilized in the process to the point where the container is sealed.
- ii. For non-filterable formulations, any additional aseptic steps should be covered.
- iii. Where aseptic manufacturing is performed under an inert atmosphere, the inert gas should be substituted with air in the process simulation unless anaerobic simulation is intended.
- iv. Processes requiring the addition of sterile powders should use an acceptable surrogate material in the same containers as those used in the process under evaluation.
- v. Separate simulations of individual unit operations (for example, processes involving drying, blending, milling and subdivision of a sterile powder) should be avoided. Any use of individual simulations should be supported by a documented justification and ensure that the sum total of the individual simulations continues to fully cover the whole process.
- vi. The process simulation procedure for lyophilized products should represent the entire aseptic processing chain, including filling, transport, loading, a representative duration of the chamber dwell, unloading and sealing under specified, documented and justified conditions representing worst-case operating parameters.
- vii. The lyophilization process simulation should mimic all aspects of the process, except those that may affect the viability or recovery of

contaminants. For instance, boiling over or actual freezing of the solution should be avoided. Factors to consider in determining APS design include, where applicable:

- the use of air to break vacuum instead of nitrogen or other process gases;
- replicating the maximum interval between sterilization of the lyophilizer and its use;
- replicating the maximum period of time between filtration and lyophilization;
- quantitative aspects of worst-case situations, for example, loading the largest number of trays, replicating the longest duration of loading where the chamber is open to the environment.

9.34 The APS should take into account various aseptic manipulations and interventions known to occur during normal production, as well as worst-case situations, and should take into account the following:

- i. Inherent and corrective interventions representative of the routine process should be performed in a manner and frequency similar to that during the routine aseptic process.
- ii. The inclusion and frequency of interventions in the APS should be based on assessed risks posed to product sterility.

9.35 APS should not be used to justify practices that pose unnecessary contamination risks.

9.36 In developing the APS plan, consideration should be given to the following:

- i. Identification of worst-case conditions covering the relevant variables, such as container size and line speed, and their impact on the process. The outcome of the assessment should justify the variables selected.
- ii. Determining the representative sizes of container or closure combinations to be used for validation. A bracketing or matrix approach may be considered for validation of the same container or closure configuration for different products where process equivalence is scientifically justified.
- iii. Maximum permitted holding times for sterile product and equipment exposed during the aseptic process.
- iv. The volume filled per container, which should be sufficient to ensure that the medium contacts all equipment and component surfaces that may directly contaminate the sterile product. The volume used should provide sufficient headspace to support potential microbial growth and ensure that turbidity can be detected during inspection.

- v. The requirement for substitution of any inert gas used in the routine aseptic manufacturing process by air unless anaerobic simulation is intended. In these situations, inclusion of occasional anaerobic simulations as part of the overall validation strategy should be considered (refer to paragraph 9.33, point iii).
- vi. The selected nutrient medium should be capable of growing a designated group of reference microorganisms, as described by the relevant pharmacopoeia, and suitably representative local isolates.
- vii. The method of detection of microbial contamination should be scientifically justified to ensure that contamination is reliably detected.
- viii. The process simulation should be of sufficient duration to simulate the process, the operators that perform interventions, shift changes, and the capability of the processing environment to provide appropriate conditions for the manufacture of a sterile product.
- ix. Where the manufacturer operates different or extended shifts, the APS should be designed to capture factors specific to those shifts that are assessed to pose a risk to product sterility; for example, the maximum duration for which an operator may be present in the cleanroom.
- x. Simulating normal aseptic manufacturing interruptions where the process is idle (for example, shift changeovers, recharging dispensing vessels, introduction of additional equipment).
- xi. Ensuring that environmental monitoring is conducted as required for routine production, and throughout the entire duration of the process simulation.
- xii. Where campaign manufacturing occurs, as in the use of barrier technologies or manufacture of sterile active substances, consideration should be given to designing and performing the process simulation so that it simulates the risks associated with both the beginning and the end of the campaign and demonstrating that the campaign duration does not pose any risk.
- xiii. The performance of end of production or campaign APS may be used for additional assurance or investigative purposes; however, their use should be justified in the CCS and should not replace routine APS. If used, it should be demonstrated that any residual product does not negatively impact the recovery of any potential microbial contamination.

9.37 For sterile active substances, batch size should be large enough to represent routine operation, simulate intervention operation at the worst case and cover all surfaces that may come into contact with the sterile product. In addition, all the simulated materials (surrogates or growth medium) should be subjected to

microbial evaluation. The simulation materials should be sufficient to satisfy the evaluation of the process being simulated and should not compromise the recovery of microorganisms.

- 9.38 APS should be performed as part of the initial validation, with at least three consecutive satisfactory simulation tests that cover all working shifts that the aseptic process may occur in, and after any significant modification to operational practices, facilities, services or equipment that are assessed to have an impact on the sterility assurance of the product (such as modification to the HVAC system or equipment, changes to process, number of shifts and numbers of personnel, or major facility shutdown). Normally, APS (periodic revalidation) should be repeated twice a year (approximately every six months) for each aseptic process, each filling line and each shift. Each operator should participate in at least one successful APS annually. Consideration should be given to performing an APS after the last batch prior to shutdown, before long periods of inactivity or before decommissioning or relocation of a line.
- 9.39 Where manual operation (such as aseptic compounding or filling) occurs, each type of container, container closure and equipment train should be initially validated, with each operator participating in at least three consecutive successful APS and revalidated with one APS approximately every six months for each operator. The APS batch size should mimic that used in the routine aseptic manufacturing process.
- 9.40 The number of units processed (filled) for APS should be sufficient to effectively simulate all activities that are representative of the aseptic manufacturing process. Justification for the number of units to be filled should be clearly captured in the CCS. Typically, a minimum of 5000 to 10 000 units should be filled. For small batches (for example, those under 5000 units), the number of containers for APS should at least equal the size of the production batch.
- 9.41 Filled APS units should be agitated, swirled or inverted before incubation to ensure contact of the medium with all interior surfaces in the container. All integral units from the APS should be incubated and evaluated, including units with cosmetic defects or those that have gone through non-destructive in-process control checks. If units are discarded during the process simulation and not incubated, these should be comparable with units discarded during a routine fill, and only if production standard operating procedures clearly specify that units must be removed under the same circumstances (that is, type of intervention, line location and specific number of units removed). In no case should more units be removed during an APS intervention than would be cleared during a production run. Examples may include those that must be discarded during routine production after the set-up process or following a specific type of intervention. To fully understand the process

and assess contamination risks during aseptic set-up or mandatory line clearances, these units would typically be incubated separately, and would not necessarily be included in the acceptance criteria for the APS.

- 9.42 Where processes include materials that contact the product contact surfaces but are then discarded (such as product flushes), the discarded material should be simulated with nutrient media and be incubated as part of the APS unless it can be clearly demonstrated that this waste process would not impact the sterility of the product.
- 9.43 Filled APS units should be incubated in a clear container to ensure visual detection of microbial growth. Where the product container is not clear (such as amber glass or opaque plastic), clear containers of identical configuration may be substituted to aid in the detection of contamination. When a clear container of identical configuration cannot be substituted, a suitable method for the detection of microbial growth should be developed and validated. Microorganisms isolated from contaminated units should be identified to the species level when practical, to assist in the determination of the likely source of the contaminant.
- 9.44 Filled APS units should be incubated without delay to achieve the best possible recovery of potential contamination. The selection of the incubation conditions and duration should be scientifically justified and validated to provide an appropriate level of sensitivity of detection of microbial contamination.
- 9.45 On completion of incubation:
- i. Filled APS units should be inspected by personnel who have been appropriately trained and qualified for the detection of microbiological contamination. Inspection should be conducted under conditions that facilitate the identification of any microbial contamination.
 - ii. Samples of the filled units should undergo positive control by inoculation with a suitable range of reference organisms and suitably representative local isolates.
- 9.46 The target should be zero growth. Any contaminated unit should result in a failed APS and the following actions should be taken.
- i. An investigation should be undertaken to determine the most probable root causes.
 - ii. Appropriate corrective measures should be determined and implemented.
 - iii. A sufficient number of successful, consecutive repeat APS (normally a minimum of three) should be conducted in order to demonstrate that the process has been returned to a state of control.

- iv. A prompt review should be made of all appropriate records relating to aseptic production since the last successful APS;
 - v. The outcome of the review should include a risk assessment of potential sterile breaches in batches manufactured since the last successful APS.
 - vi. All other batches not released to the market should be included in the scope of the investigation. Any decision regarding their release status should consider the investigation outcome.
 - vii. All products that have been manufactured on a line subsequent to a process simulation failure should be quarantined until a successful resolution of the process simulation failure has occurred.
 - viii. Where the root cause investigation indicates that the failure was related to operator activity, actions to limit the operator's activities, until retrained and requalified, should be taken.
 - ix. Production should resume only after completion of successful revalidation.
- 9.47 All APS runs should be fully documented and include a reconciliation of units processed (such as units filled, incubated and not incubated). The justification for filled and non-incubated units should be included in the documentation. All interventions performed during the APS should be recorded, including the start and end time of each intervention and the involved person. All microbial monitoring data, as well as other testing data, should be recorded in the APS batch record.
- 9.48 An APS run should be aborted only under circumstances in which written procedures require commercial lots to be equally handled. An investigation should be documented in such cases.
- 9.49 An aseptic process should be subject to a repeat of the initial validation when:
- i. the specific aseptic process has not been in operation for an extended period of time;
 - ii. there is a change to the process, equipment, procedures or environment that has the potential to affect the aseptic process or an addition of new product containers or container-closure combinations.
- 9.50 Routine production, after completion of the APS, should only commence after validated procedures have been completed in accordance with the CCS, to ensure that there is no risk to the product.

10. Quality control

Note: This section mainly focuses on some aspects of microbiological control. See also *WHO good practices for pharmaceutical microbiology laboratories* (Annex 2, WHO Technical Report Series 961, 2011) and relevant pharmacopoeia.

- 10.1 There should be a sufficient number of personnel available with appropriate training and experience in microbiology, sterility assurance and knowledge of the processes to support the design of the manufacturing activities, environmental monitoring regime and any investigation needed to assess the impact of microbiologically linked events on the quality and safety of the sterile product.
- 10.2 Specifications for raw materials, components and products should include requirements for microbial, particulate and endotoxin/pyrogen limits when the need for this has been indicated by monitoring or by the CCS.
- 10.3 The bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilized products and the results considered as part of the final batch review. There should be defined limits for bioburden immediately before the final sterilizing grade filter or the terminal sterilization process, which are related to the efficiency of the method to be used. Samples should be taken to be representative of the worst-case scenario (for example, at the end of hold time). Where overkill sterilization parameters are set for terminally sterilized products, bioburden should be monitored at suitable scheduled intervals.
- 10.4 For products authorized for parametric release, a supporting presterilization bioburden monitoring programme for the filled product prior to initiating the sterilization cycle should be developed and the bioburden assay should be performed for each batch. The sampling locations of filled units before sterilization should be based on a worst-case scenario and be representative of the batch. Any organisms found during bioburden testing should be identified and their impact on the effectiveness of the sterilizing process determined. Where appropriate, the level of endotoxin/pyrogen should be monitored.
- 10.5 The sterility test applied to the finished product should only be regarded as the last in a series of critical control measures by which sterility is assured. It cannot be used to assure sterility of a product that does not meet its design, procedural or validation parameters. The test should be validated for the product concerned.
- 10.6 The sterility test should be performed under aseptic conditions. Samples taken for sterility testing should be representative of the whole of the batch but should, in particular, include samples taken from parts of the batch considered to be most at risk of contamination, for example:

- i. For products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch. Additional samples (for example, taken after critical interventions) should be considered based on risk.
- ii. For products that have been heat sterilized in their final containers, samples taken should be representative of the worst-case locations (for example, the potentially coolest or slowest to heat part of each load).
- iii. For products that have been lyophilized, samples should be taken from different lyophilization loads.

Note: Where the manufacturing process results in sub-batches (for example, for terminally sterilized products), then sterility samples from each sub-batch should be taken and a sterility test for each sub-batch performed. (Consideration should also be given to performing separate testing for the other parameters of the product.)

- 10.7 For some products, it may not be possible to obtain a sterility test result prior to release because the shelf-life of the product is too short to allow completion of a sterility test. In these cases, the additional considerations of design of the process and additional monitoring or alternative test methods required to mitigate the identified risks should be assessed and documented.
- 10.8 Any substance or process (for example, vaporized hydrogen peroxide, ultraviolet) used to decontaminate the external surfaces of sterility samples prior to testing should not negatively impact the sensitivity of the test method or the reliability of the outcome of the test.
- 10.9 Media used for product testing should be quality control tested according to the relevant pharmacopoeia before use. Media used for environmental monitoring and APS should be tested for growth promotion before use, using a scientifically justified and designated group of reference microorganisms and including suitably representative in-house isolates. Media quality control testing should normally be performed by the end user. Any reliance on outsourced testing or supplier testing of media should be justified and transportation and shipping conditions should be thoroughly considered in this case.
- 10.10 Environmental monitoring data and trend data generated for classified areas should be reviewed as part of product batch certification and release. A written procedure should be available that describes the actions to be taken when data from environmental monitoring are found out of trend or exceeding the established limits. For products with a short shelf-life, the environmental data for the time of manufacture may not be available; in these cases, the compliance

should include a review of the most recent available data. Manufacturers of these products should consider the use of rapid or alternative methods.

10.11 Rapid and automated microbial methods should be validated.

Glossary

action limit. An established relevant measure (for example, microbial or airborne particle limits) that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.

airlock. An enclosed space with interlocked doors, constructed to maintain air pressure control between adjoining rooms (generally with different air cleanliness standards). The intent of an airlock is to preclude ingress of particle matter and microorganism contamination from a less controlled area.

alert level. An established relevant measure (such as microbial or airborne particle levels) giving early warning of potential drift from normal operating conditions and validated state, which does not necessarily give grounds for corrective action but triggers appropriate scrutiny and follow-up to address the potential problem. Alert levels are established based on routine and qualification trend data and are periodically reviewed. The alert level can be based on a number of parameters, including adverse trends, individual excursions above a set limit and repeat events.

asepsis. A state of control attained by using an aseptic work area and performing activities in a manner that precludes microbial contamination of the exposed sterile product.

aseptic preparation or processing. The handling of sterile product, containers or devices in a controlled environment in which the air supply, materials and personnel are regulated to prevent microbial, endotoxin/pyrogen and particle contamination.

aseptic process simulation (APS). A simulation of the entire aseptic manufacturing process in order to verify the capability of the process to ensure product sterility. APS includes all aseptic operations associated with routine manufacturing (for example, equipment assembly, formulation, filling, lyophilization and sealing processes, as necessary).

bacterial retention testing. This test is performed to validate that a filter can remove bacteria from a gas or liquid. The test is usually performed using a standard organism, such as *Brevundimonas diminuta*, at a minimum concentration of 10⁷ colony-forming units/cm².

barrier. A physical partition that affords aseptic processing area (usually grade A) protection by separating it from the background environment. Such systems frequently use in part or totally the barrier technologies known as RABS (restricted access barrier systems) or isolators.

bioburden. The total number of microorganisms associated with a specific item, such as personnel, manufacturing environments (air and surfaces), equipment, product packaging, raw materials (including water), in-process materials or finished products.

biodecontamination. A process that eliminates viable bioburden via the use of sporicidal chemical agents.

biological indicator. A population of microorganisms inoculated onto a suitable medium (for example, solution, container or closure) and placed within a sterilizer or load or room location to determine the sterilization or disinfection cycle efficacy of a physical or chemical process. The challenge microorganism is selected and validated based upon its resistance to the given process. Incoming lot D-value, microbiological count and purity define the quality of the biological indicator.

blow-fill-seal (BFS). A technology in which containers are formed from a thermoplastic granulate, filled with product, and then sealed in a continuous, integrated, automatic operation. The two most common types of BFS machines are the shuttle type (with parison cut) and the rotary type (closed parison).

campaign manufacture. The manufacture of a series of batches of the same product in sequence in a given period of time with strict adherence to established and validated control measures.

classified area. An area that contains a number of cleanrooms [see also cleanroom definition].

clean area. An area with defined particle and microbiological cleanliness standards, usually containing a number of joined cleanrooms.

cleaning. A process for removing contamination (for example, product residues or disinfectant residues).

cleanroom. A room designed, maintained and controlled to prevent particle and microbial contamination of drug products. Such a room is assigned and reproducibly meets an appropriate air cleanliness level.

cleanroom classification. A method of assessing the level of air cleanliness against a specification for a cleanroom or clean air equipment by measuring the total particle concentration.

cleanroom qualification. A method of assessing the level of compliance of a classified cleanroom or clean air equipment with its intended use.

closed system. A system in which the product is not exposed to the surrounding environment. For example, this can be achieved by the use of bulk product holders (such as tanks or bags) that are connected to each other by pipes or tubes as a system. Where used for sterile products, the full system is sterilized after the connections are made. Examples of these can be large-scale reusable systems, such as those seen in active substance manufacturing, or disposable bag and manifold systems, such as those seen in the manufacture of biological products. Closed systems are not opened until the conclusion of an operation. The use of the term “closed systems” in this guideline does not refer to systems such as RABS or isolator systems.

colony-forming unit (CFU). A microbiological term that describes a single detectable colony that originates from one or more microorganisms. CFUs are typically expressed as CFU per millilitre (mL) for liquid samples, CFU per square metre (m³) for air samples and CFU per sample for samples captured on solid medium, such as settle or contact plates.

contamination. The undesired introduction of impurities of a microbiological nature (quantity and type of microorganisms, pyrogen) or of foreign particle matter into or onto a raw material, intermediate, active substance or drug product during production, sampling, packaging or repackaging, storage or transport with the potential to adversely impact product quality.

contamination control strategy (CCS). A planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

corrective intervention. An intervention that is performed to correct or adjust an aseptic process during its execution. This may not occur at a set frequency in the routine aseptic process. Examples include clearing component jams, stopping leaks, adjusting sensors and replacing equipment components.

critical intervention. An intervention (corrective or inherent) into the critical zone.

critical surface. A surface that may come directly into contact with, or directly affect, a sterile product or its containers or closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation and sterility is maintained throughout processing.

critical zone. A location within the aseptic processing area in which product and critical surfaces are exposed to the environment.

dead leg. Length of non-circulating pipe (where fluid may remain static) that is greater than three internal pipe diameters.

decommission. To close and remove from use a process, equipment or cleanroom.

decontamination. The overall process of removal or reduction of any contaminants (chemical, waste, residue or microorganisms) from an area, object or person. The method of decontamination used (for example, cleaning, disinfection, sterilization) should be chosen and validated to achieve a level of cleanliness appropriate to the intended use of the item decontaminated [see also biodecontamination].

depyrogenation. A process designed to remove or inactivate pyrogenic material (such as endotoxin) to a specified minimum quantity.

disinfection. The process by which a reduction of the number of microorganisms is achieved by the irreversible action of a product on their structure or metabolism to a level deemed to be appropriate for a defined purpose.

D-value. The value of a parameter of sterilization (duration or absorbed dose) required to reduce the number of viable organisms to 10% of the original number.

endotoxin. A pyrogenic product (lipopolysaccharide) present in the Gram-negative bacterial cell wall. Endotoxin can lead to reactions in patients receiving injections ranging from fever to death.

equilibration time. The period that elapses between the attainment of the sterilization temperature at the reference measurement point and the attainment of the sterilization temperature at all points within the load.

extractable. A chemical entity that migrates from the surface of the process equipment, exposed to an appropriate solvent at extreme conditions, into the product or material being processed.

filter integrity test. A test to confirm that a filter (product, gas, or heating, ventilation and air-conditioning (HVAC) filter) retains its retentive properties and has not been damaged during handling, installation or processing.

first air. Filtered air that has not been interrupted prior to contacting exposed product and product contact surfaces with the potential to add contamination to the air prior to reaching the critical zone.

form-fill-seal (FFS). An automated filling process, typically used for terminally sterilized products, that constructs the primary container out of a continuous flat roll

of packaging film while simultaneously filling the formed container with product and sealing the filled containers in a continuous process. FFS processes may utilize a single web system (whereby a single flat roll of film is wrapped around itself to form a cavity) or a dual web system (whereby two flat rolls of film are brought together to form a cavity), often with the aid of vacuum moulds or pressurized gases. The formed cavity is filled, sealed and cut into sections. Films typically consist of a polymeric material, polymeric coated foil or other suitable material.

gowning qualification. A programme that establishes, both initially and on a periodic basis, the capability of an individual to don the complete gown.

grade A air supply. Air that is passed through a filter qualified as capable of producing grade A total particle quality air, but where there is no requirement to perform continuous total particle monitoring or meet grade A viable monitoring limits. Specifically used for the protection of fully stoppered vials where the cap has not yet been crimped.

high-efficiency particulate air (HEPA) filter. A high-efficiency particulate air filter specified in accordance with a relevant international standard.

inherent intervention. An intervention that is an integral part of the aseptic process and is required for set-up, routine operation or monitoring (for example, aseptic assembly, container replenishment or environmental sampling). Inherent interventions are required by procedure or work instruction for the execution of the aseptic process.

intrinsic sterile connection device. A device that reduces the risk of contamination during the connection process. The device can be mechanical or fusion sealing.

isokinetic sampling head. A sampling head designed to disturb the air as little as possible so that the same particles go into the nozzle as would have passed the area if the nozzle had not been there (that is, the sampling condition in which the mean velocity of the air entering the sample probe inlet is nearly the same ($\pm 20\%$) as the mean velocity of the airflow at that location).

isolator. An enclosure capable of being subject to reproducible interior biodecontamination, with an internal work zone meeting grade A conditions that provide uncompromised continuous isolation of its interior from the external environment (for example, surrounding cleanroom air and personnel). There are two major types of isolators:

- Closed isolator systems exclude external contamination of the isolator's interior by accomplishing material transfer via aseptic connection to auxiliary equipment rather than use of openings to the surrounding environment. Closed systems remain sealed throughout operations.

- Open isolator systems are designed to allow for the continuous or semicontinuous ingress or egress of materials during operations through one or more openings. Openings are engineered (for example, using continuous overpressure) to exclude the entry of external contaminant into the isolator.

leachable. A chemical entity that migrates into a product from the product contact surface of the process equipment or containers under normal condition of use or storage.

local isolates. Suitably representative microorganisms of the site that are frequently recovered through environmental monitoring within the classified zone or areas (especially grade A and B areas), personnel monitoring, or positive sterility test results.

lyophilization. A physical-chemical drying process designed to remove solvents, by way of sublimation, from both aqueous and non-aqueous systems, primarily to achieve product or material stability. Lyophilization is synonymous with the term “freeze-drying”.

manual aseptic processing. An aseptic process whereby the operator manually compounds, fills, places or seals an open container with sterile product.

operator. Any individual participating in the processing operation, including line set-up, filling, maintenance or other personnel associated with manufacturing activities.

overkill sterilization. A process that is sufficient to provide at least a $12 \log_{10}$ reduction of microorganisms having a minimum D-value of 1 minute.

parison. The “tube” of polymer extruded by the BFS machine from which containers are formed.

pass-through hatch. Synonymous with airlock [refer to airlock definition] but typically smaller in size.

patient. Human or animal participant in a clinical trial.

post-aseptic processing terminal heat treatment. A terminal moist heat process employed after aseptic processing that has been demonstrated to provide a sterility assurance level of $\leq 10^{-6}$ but where the requirements of steam sterilization (for example, $F_0 \geq 8$ minutes) are not fulfilled. This may also be beneficial in the destruction of viruses that may not be removed through filtration.

pyrogen. A substance that induces a febrile reaction in patients receiving injections.

rapid transfer system or port. A system used for the transfer of items into RABS or isolators that minimizes the risk to the critical zone. An example would be a rapid transfer container with an alpha/beta port.

raw material. Any ingredient intended for use in the manufacture of a sterile product, including those that may not appear in the final drug product.

restricted access barrier system (RABS). A system that provides an enclosed, but not fully sealed, environment meeting defined air quality conditions (for aseptic processing grade A) and using a rigid wall enclosure and integrated gloves to separate its interior from the surrounding cleanroom environment. The inner surfaces of the RABS are disinfected and decontaminated with a sporicidal agent. Operators use gloves, half suits, rapid transfer systems or ports, and other integrated transfer ports to perform manipulations or convey materials to the interior of the RABS. Depending on the design, doors are rarely opened and only under strictly predefined conditions.

single-use system (SUS). A system in which product contact components are used only once to replace reusable equipment such as stainless steel transfer lines or bulk containers. Single-use systems covered in this document are those that are used in manufacturing processes of sterile products and are typically made up of disposable components such as bags, filters, tubing, connectors, storage bottles and sensors.

sporicidal agent. An agent that destroys bacterial and fungal spores when used in sufficient concentration for a specified contact time. It is expected to kill all vegetative microorganisms.

sterile product. For the purpose of this guidance, sterile product refers to one or more of the sterilized elements exposed to aseptic conditions and, ultimately, making up the sterile active substance or finished sterile product. These elements include the containers, closures and components of the finished drug product. Or, a product that is rendered sterile by a terminal sterilization process.

sterilizing grade filter. A filter that, when appropriately validated, will remove a defined microbial challenge from a fluid or gas producing a sterile effluent. Usually such filters have a pore size equal to or less than 0.22 micrometres (μm).

terminal sterilization. The application of a lethal sterilizing agent or conditions to a product in its final container to achieve a predetermined sterility assurance level of 10^{-6} or better (that is, the theoretical probability of there being a single viable microorganism present on or in a sterilized unit is equal to or less than 1×10^{-6} , or 1 in a million).

turbulent airflow. Air that is not unidirectional. Turbulent air in cleanrooms should flush the cleanroom via a mixed flow dilution and ensure maintenance of acceptable air quality.

unidirectional airflow. An airflow moving in a single direction in a robust and uniform manner and at sufficient speed to reproducibly sweep particles away from the critical processing or testing area.

unidirectional airflow unit. A cabinet supplied with filtered unidirectional airflow (previously referred to as a laminar airflow unit).

worst case. A set of conditions encompassing processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure (when compared with ideal conditions). Such conditions have the highest potential to, but do not necessarily always, result in product or process failure.

water system. A system for producing, storing and distributing water, usually compliant with a specific pharmacopoeia grade (for example, purified water and water for injection).

Z-value. The temperature difference that leads to a 10-fold change in the D-value of the biological indicator.

Further reading

- WHO good practices for pharmaceutical microbiology laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. WHO Technical Report Series No. 961, Annex 2. Geneva: World Health Organization; 2011 (<https://apps.who.int/iris/handle/10665/44079>).
- WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. WHO Technical Report Series No. 986, Annex 2. Geneva: World Health Organization; 2014 (<https://apps.who.int/iris/handle/10665/112733>).
- Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. WHO Technical Report Series No. 1010, Annex 8. Geneva: World Health Organization; 2018 (<https://apps.who.int/iris/handle/10665/272452>).
- Good manufacturing practices: guideline on validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. WHO Technical Report Series No. 1019, Annex 3. Geneva: World Health Organization; 2019 (<https://apps.who.int/iris/handle/10665/312316>).
- Production of water for injection by means other than distillation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. WHO Technical Report Series No. 1025, Annex 3. Geneva: World Health Organization; 2020 (<https://apps.who.int/iris/handle/10665/331814>).
- Water for injections [Aqua pro injection]. In: The International Pharmacopoeia, tenth edition. Geneva: World Health Organization; 2020 (<https://digicollections.net/phint/2020/index.html#d/b.6.1.364>).
- Good manufacturing practices: water for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. WHO Technical Report Series No. 1033, Annex 3. Geneva: World Health Organization; 2021 (<https://apps.who.int/iris/handle/10665/340323>).
- ISO 14644 series of standards. Geneva: International Organization for Standardization (<https://www.iso.org/search.html?q=ISO%2014644>).

3.2 WHO good manufacturing practices for biological products

(jointly with the Expert Committee on Biological Standardization)

Annex 3, WHO Technical Report Series, 996,
2016

Replacement¹ of Annex 1 of WHO Technical Report Series,
No. 822

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¹ It also replaces Annex 3 of the report of the Expert Committee on Specifications for Pharmaceutical Preparations, Technical Report Series, No. 834, and forms Annex 2 of the report of the Expert Committee on Biological Standardization, Technical Report Series, No. 993.

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Guidelines published by WHO are intended to be scientific and advisory in nature. Each of the following sections constitutes guidance for national regulatory authorities (NRAs) and for manufacturers of biological products. If an NRA so desires, these WHO Guidelines may be adopted as definitive national requirements, or modifications may be justified and made by the NRA.

Abbreviations

AEFI	adverse event following immunization
ATMP	advanced therapy medicinal product
BCG	bacille Calmette–Guérin
GMP	good manufacturing practice(s)
HEPA	high-efficiency particulate air
HVAC	heating, ventilation and air conditioning
IgE	immunoglobulin E
mAb	monoclonal antibody
MCB	master cell bank
MSL	master seed lot
MVS	master virus seed
NRA	national regulatory authority
PDL	population doubling level
PQR	product quality review
PQS	pharmaceutical quality system
QRM	quality risk management
rDNA	recombinant DNA
SPF	specific pathogen free
TSE	transmissible spongiform encephalopathy
WCB	working cell bank
WSL	working seed lot
WVS	working virus seed

1. Introduction

Biological products can be defined according to their source material and method of manufacture. The source materials and methods employed in the manufacture of biological products for human use therefore represent critical factors in shaping their appropriate regulatory control. Biological products are derived from cells, tissues or microorganisms and reflect the inherent variability characteristic of living materials. The active substances in biological products are often too complex to be fully characterized by utilizing physicochemical testing methods alone and may show a marked heterogeneity from one preparation and/or batch to the next. Consequently, special considerations are needed when manufacturing biological products in order to maintain consistency in product quality.

Good manufacturing practices (GMP) for biological products were first published by WHO in 1992 (1). This current revision reflects subsequent developments that have taken place in science and technology, and in the application of risk-based approaches to GMP (2–14). The content of this document should be considered complementary to the general recommendations set out in the current WHO good manufacturing practices for pharmaceutical products: main principles (2) and in other WHO documents related specifically to the production and control of biological products.

This document is intended to serve as a basis for establishing national guidelines for GMP for biological products. If a national regulatory authority (NRA) so desires, the guidance provided may be adopted as definitive national requirements, or modifications may be justified and made by the NRA in light of the risk–benefit balance and legal considerations in each authority. In such cases, it is recommended that any modification to the principles and technical specifications set out below should be made only on the condition that the modifications ensure product quality, safety and efficacy that are at least equivalent to that recommended in this document.

2. Scope

The guidance provided in this document applies to the manufacture, control and testing of biological products for human use – from starting materials and preparations (including seed lots, cell banks and intermediates) to the finished product.

Manufacturing procedures within the scope of this document include:

- growth of strains of microorganisms and eukaryotic cells;
- extraction of substances from biological tissues, including human, animal and plant tissues, and fungi;
- recombinant DNA (rDNA) techniques;
- hybridoma techniques;
- propagation of microorganisms in embryos or animals.

Medicinal products of biological origin manufactured by these procedures include allergens, antigens, vaccines, certain hormones, cytokines, monoclonal antibodies (mAbs), enzymes, animal immune sera, products of fermentation (including products derived from rDNA), biological diagnostic reagents for in vivo use and advanced therapy medicinal products (ATMPs) used for example in gene therapy and cell therapy.

For human whole blood, blood components and plasma-derived products for therapeutic use separate comprehensive WHO guidance is available and should be followed (12, 15).

In some countries certain small-molecule medicinal products (for example, antibiotics) are not defined as biological products. Nevertheless, where the manufacturing procedures described in this document are used then the guidance provided may be followed.

The preparation of investigational medicinal products for use in clinical trials should follow the basic principles of GMP set out in these and other WHO GMP guidelines (2, 16) as appropriate. However, certain other requirements (such as process and analytical method validations) could be completed before marketing authorization (17–19).

The current document does not provide detailed recommendations for specific classes of biological products (for example, vaccines). Attention is therefore directed to other relevant WHO documents, and in particular to WHO recommendations to assure the quality, safety and efficacy of specific products.²

Table 1 illustrates the typical risk-based application of the current document (4, 7). It should be noted that this table is illustrative only and is not intended to describe the precise scope.

² See: <http://www.who.int/biologicals/en/> (accessed 4 November 2015).

Table A3.1
Scope of the current document (illustrative)

Type and source of material	Example products	Application of this document to steps in manufacture
1. Animal or plant sources: non-transgenic	Heparins, insulin, enzymes, proteins, allergen extract, ATMPs, animal immune sera	Collection of plant, organ, tissue or fluid Cutting, mixing and/or initial processing Isolation and purification Formulation and filling
2. Virus or bacteria/fermentation/cell culture	Viral or bacterial vaccines, enzymes, proteins	Establishment and maintenance of MCB, WCB, MSL/MS, WSL/WVS Cell culture and/or fermentation Inactivation when applicable, isolation and purification Formulation and filling
3. Biotechnology fermentation/cell culture	Recombinant products, mAbs, allergens, vaccines, gene therapy (viral and non-viral vectors, plasmids)	Establishment and maintenance of MCB, WCB, MSL, WSL Cell culture and/or fermentation Isolation, purification and modification Formulation and filling
4. Animal sources: transgenic	Recombinant proteins, ATMPs	Master and working transgenic bank Collection, cutting, mixing and/or initial processing Isolation, purification and modification Formulation and filling
5. Plant sources: transgenic	Recombinant proteins, vaccines, allergens	Master and working transgenic bank Growing and/or harvesting Initial extraction, isolation, purification and modification Formulation and filling

Table A3.1 *continued*

Type and source of material	Example products	Application of this document to steps in manufacture		
6. Human sources	Urine-derived enzymes, hormones	Collection of fluid Mixing and/or initial processing Isolation and purification Formulation and filling		
7. Human and/or animal sources	Gene therapy: genetically modified cells Somatic cell therapy	Donation, procurement and testing of starting tissue/cells ^a Donation, procurement and testing of starting tissue/cells ^a Tissue-engineered products	Vector manufacture and cell purification and processing Establishing and maintaining MCB, WCB or cell stock Initial processing, isolation and purification, establishing and maintaining MCB, WCB, primary cell stock Ex vivo genetic modification of cells, establish MCB, WCB or cell stock Cell isolation, culture purification and combination with non-cellular components Cell isolation, culture, purification and combination with non-cellular components	Ex vivo genetic modification of cells, establish MCB, WCB or cell stock Cell isolation, culture purification and combination with non-cellular components Formulation, combination and filling Formulation, combination and filling

^a GMP guidelines, as described in this document, are not applied to this step. Other national regulations, requirements, recommendations and/or guidelines may apply as deemed necessary by the NRA.

MCB = master cell bank; MSL = master seed lot; MVS = master virus seed; WCB = working cell bank; WSL = working seed lot; WVS = working virus seed.

3. Terminology

In addition to the terms defined in WHO good manufacturing practices for pharmaceutical products: main principles (2) and WHO good manufacturing practices for sterile pharmaceutical products (3), the definitions given below apply to the terms as used in the current document. These terms may have different meanings in other contexts.

Active substance: a defined process intermediate containing the active ingredient, which is subsequently formulated with excipients to produce the drug product. This may also be referred to as “drug substance” or “active ingredient” in other documents.

Adventitious agents: contaminating microorganisms of the cell culture or source materials, including bacteria, fungi, mycoplasmas/spiroplasmas, mycobacteria, rickettsia, protozoa, parasites, transmissible spongiform encephalopathy (TSE) agents and viruses that have been unintentionally introduced into the manufacturing process of a biological product. The source of these contaminants may be the legacy of the cell line, or the raw materials used in the culture medium to propagate the cells (in banking, in production or in their legacy), the environment, personnel, equipment or elsewhere.

Allergen: a molecule capable of inducing an immunoglobulin E (IgE) response and/or a Type I allergic reaction.

Antibodies: proteins produced naturally by the B-lymphocytes that bind to specific antigens. Using rDNA technology antibodies are also produced in other (continuous) cell lines. Antibodies may be divided into two main types – monoclonal and polyclonal antibodies – based on key differences in their methods of manufacture. Also called immunoglobulins.

Antigens: substances (for example, toxins, foreign proteins, bacteria, tissue cells and venoms) capable of inducing specific immune responses.

Axenic: a single organism in culture which is not contaminated with any other organism.

Bioburden: the level and type (objectionable or not) of microorganisms present in raw materials, media, biological substances, intermediates or finished products. Regarded as contamination when the level and/or type exceed specifications.

Biohazard: any biological material considered to be hazardous to people and/or the environment.

Biological starting materials: starting materials derived from a biological source that mark the beginning of the manufacturing process of a drug, as described in a marketing authorization or licence application, and from which the active ingredient is derived either directly (for example, plasma derivatives, ascitic fluid and bovine lung) or indirectly (for example, cell substrates, host/vector production cells, eggs and viral strains).

Biosafety risk group: denotes the containment conditions required for safe handling of organisms associated with different hazards, ranging from Risk Group 1

(lowest risk, no or low individual and community risk, and unlikely to cause disease) to Risk Group 4 (highest risk, high individual and community risk, usually causes severe disease, and which is likely to spread with no prophylaxis or treatment available) (20).

Campaign manufacture: the manufacture of an uninterrupted sequence of batches of the same product or intermediate in a given time period, followed by strict adherence to accepted control measures before switching to another product or different serotype. The different products are not run at the same time but may be run on the same equipment.

Cell bank: a collection of appropriate containers whose contents are of uniform composition and stored under defined conditions. Each container represents an aliquot of a single pool of cells.

Cell culture: the process by which cells that are no longer organized into tissues are grown in vitro under defined and controlled conditions. Cell cultures are operated and processed under axenic conditions to ensure a pure culture absent of microbial contamination.

Cell stock: primary cells expanded to a given number of cells to be aliquoted and used as starting material for production of a limited number of lots of a cell-based medicinal product.

Containment: the concept of using a process, equipment, personnel, utilities, system and/or facility to contain product, dust or contaminants in one zone, preventing them from entering into another zone and/or escaping.

Continuous culture: a process by which the growth of cells is maintained by periodically replacing a portion of the cells and the medium so that there is no lag or saturation phase.

Control strategy: a planned set of controls derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance and finished product materials and components; facility and equipment operating conditions; in-process controls; finished product specifications; and the associated methods and frequency of monitoring and control.

Cross-contamination: contamination of a starting material, intermediate product or finished product with another starting material or product during production. In multi-product facilities, cross-contamination can occur throughout the manufacturing process, from generation of the master cell bank (MCB) and working cell bank (WCB) to finished product.

Dedicated: facility, personnel, equipment or piece of equipment used only in the manufacture of a particular product or group of specified products of similar risk.

Dedicated area: an area that may be in the same building as another area but which is separated by a physical barrier and which has, for example, separate entrances, staff facilities and air-handling systems. Also referred to as “self-contained facility” in other GMP documents.

Feeder cells: cells used in co-culture to maintain pluripotent stem cells. For human embryonic stem cell culture, typical feeder layers include mouse embryonic fibroblasts or human embryonic fibroblasts that have been treated to prevent them from dividing.

Finished product: a finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling. Also referred to as “finished dosage form”, “drug product” or “final product” in other documents.

Fermentation: maintenance or propagation of microbial cells in vitro (fermenter). Fermentation is operated and progressed under axenic conditions to ensure a pure culture absent of contaminating microorganisms.

Harvesting: the procedure by which the cells, inclusion bodies or crude supernatants containing the unpurified active ingredient are recovered.

Hybridoma: an immortalized cell line that secretes desired (monoclonal) antibodies and which is typically derived by fusing B-lymphocytes with tumour cells.

Inactivation: removal or reduction to an acceptable limit of infectivity of microorganisms or detoxification of toxins by chemical or physical modification.

Master cell bank (MCB): a quantity of well-characterized cells of animal or other origin, derived from a cell seed at a specific population doubling level (PDL) or passage level, dispensed into multiple containers and stored under defined conditions. The MCB is prepared from a single homogeneously mixed pool of cells. In some cases, such as genetically engineered cells, the MCB may be prepared from a selected cell clone established under defined conditions. However, the MCB may not be clonal. The MCB is used to derive a working cell bank (WCB).

Monoclonal antibodies (mAbs): homogenous antibody population obtained from a single clone of lymphocytes or by recombinant technology and which bind to a single epitope.

Pharmaceutical quality system (PQS): management system used by a pharmaceutical company to direct and control its activities with regard to quality.

Polyclonal antibodies: antibodies derived from a range of lymphocyte clones and produced in humans and animals in response to the epitopes on most “non-self” molecules.

Primary containment: a system of containment that prevents the escape of a biological agent into the immediate working environment. It involves the use of closed containers or biological safety cabinets along with secure operating procedures.

Quality risk management (QRM): a systematic process for the assessment, control, communication and review of risks to the quality of pharmaceutical products across the product life-cycle.

Reference sample: a sample of a batch of starting material, packaging material, intermediate or finished product which is stored for the purpose of being analysed should the need arise during the shelf-life of the batch concerned.

Retention sample: a sample of a fully packaged unit from a batch of finished product. It is stored for identification purposes (for example, of presentation, packaging,

labelling, patient information leaflet, batch number and expiry date) should the need arise during the shelf-life of the batch concerned.

Seed lot: a quantity of live cells or viruses which has been derived from a single culture (though not necessarily clonal), has a uniform composition and is aliquoted into appropriate storage containers from which all future products will be derived, either directly or via a seed lot system. The following derived terms are used in this document – master seed lot (MSL): a lot or bank of cells or viruses from which all future vaccine production will be derived. The MSL represents a well-characterized collection of cells or viruses or bacteria of uniform composition. Also referred to as “master virus seed” (MVS) for virus seeds, “master seed bank”, “master seed antigen” or “master transgenic bank” in other documents; and working seed lot (WSL): a cell or viral or bacterial seed lot derived by propagation from the MSL under defined conditions and used to initiate production of vaccines on a lot-by-lot basis. Also referred to as “working virus seed” (WVS) for virus seeds, “working seed bank”, “working seed antigen” or “working transgenic bank” in other documents.

Specific pathogen free (SPF): denoting animals or animal materials (such as chickens, embryos, eggs or cell cultures) derived from groups of animals (for example, flocks or herds) free from specified pathogens, and used for the production or quality control of biological products. Such flocks or herds are defined as animals sharing a common environment and having their own caretakers who have no contact with non-SPF groups.

Starting materials: any substances of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials. In the context of biological products manufacturing, examples of starting materials may include cryoprotectants, feeder cells, reagents, growth media, buffers, serum, enzymes, cytokines, growth factors and amino acids.

Transgenic: denoting an organism that contains a foreign gene in its normal genetic component for the expression of biological pharmaceutical materials.

Vaccine: a preparation containing antigens capable of inducing an active immune response for the prevention, amelioration or treatment of infectious diseases.

Working cell bank (WCB): a quantity of well-characterized cells of animal or other origin, derived from an MCB at a specific PDL or passage level, dispensed into multiple containers and stored under defined conditions. The WCB is prepared from a single homogeneously mixed pool of cells (often, this is the MCB). One or more of the WCB containers is used for each production culture.

4. Principles and general considerations

The manufacture of biological products should be undertaken in accordance with the basic principles of GMP. The points covered by the current document should, therefore, be considered as complementary to the general recommendations set out in the current

WHO good manufacturing practices for pharmaceutical products: main principles (2) and associated specialized guidelines and recommendations (3, 4, 10, 13, 14) as well as other WHO documents related specifically to the production and control of biological products established by the WHO Expert Committee on Biological Standardization.³

The manufacture, control and administration of biological active substances and finished products require certain specific considerations and precautions arising from the nature of these products and their processes. Unlike conventional pharmaceutical products which are manufactured using chemical and physical techniques capable of a high degree of consistency, the manufacture of biological active substances and finished products involves biological processes and materials, such as cultivation of cells or extraction from living organisms. As these biological processes may display inherent variability, the range and nature of by-products may also be variable. As a result, quality risk management (QRM) principles are particularly important for this class of materials and should be used to develop the control strategy across all stages of manufacture so as to minimize variability and reduce the opportunity for contamination and cross-contamination.

Materials and processing conditions used in cultivation processes are designed to provide conditions for the growth of target cells and microorganisms – therefore, extraneous microbial contaminants have the opportunity to grow. Furthermore, many biological products have limited ability to withstand certain purification techniques, particularly those designed to inactivate or remove adventitious viral contaminants. The design of the processes, equipment, facilities, utilities, the conditions of preparation and addition of buffers and reagents, sampling, and training of the operators are key considerations in minimizing such contamination events. Specifications outlined in WHO guidelines and recommendations will determine whether and to what stage of production substances and materials can have a defined level of bioburden or need to be sterile. Similarly, manufacturing should be consistent with other specifications set out in the product summary files, marketing authorization or clinical trial approvals (for example, number of generations (expressed as doublings or passages) between the seed lot or cell bank and the finished product).

Many biological materials (such as live-attenuated bacteria and viruses) cannot be terminally sterilized by heat, gas or radiation. In addition, some products, such as certain live and adjuvanted vaccines (for example, bacille Calmette–Guérin (BCG) or cholera), may not be sterilized by filtration processes. For these axenic products, processing should be conducted aseptically to minimize the introduction of contaminants from the point where a potential contamination cannot be removed from the manufacturing process. Relevant WHO documents should be consulted on the validation of specific manufacturing steps such as virus removal or inactivation (21).

³ See: <http://www.who.int/biologicals/en/> (accessed 4 November 2015).

Robust environmental controls and monitoring and, wherever feasible, in situ cleaning and sterilization systems, together with the use of closed systems can significantly reduce the risk of accidental contamination and cross-contamination.

Control usually involves biological analytical techniques, which typically have a greater variability than physicochemical determinations. The combination of variability in starting materials and the potential for subtle changes during the manufacturing process of biological products also requires an emphasis on production consistency. This is of particular concern because of the need to link consistency to original clinical trials documenting the product's safety and efficacy. A robust manufacturing process is therefore crucial and in-process controls take on a particular importance in the manufacture of biological active substances and medicinal products.

Because of the risks inherent in producing and manipulating pathogenic and transmissible microorganisms during the production and testing of biological materials, GMP should prioritize the safety of the recipient to whom the biological product is administered, the safety of personnel during operation and the protection of the environment.

Biosafety considerations should follow national guidelines and (if applicable and available) international guidelines. In most countries, the regulation of GMP and biosafety are governed by different institutions. In the context of manufacturing pathogenic biological products of Biosafety Risk Group 3 and 4, close collaboration between such institutions is especially required to assure that both product contamination and environmental contamination levels are controlled within acceptable limits. Specific recommendations regarding containment are outlined below in section 10.

5. Pharmaceutical quality system and quality risk management

Biological products, like any pharmaceutical product, should be manufactured in accordance with the requirements of a pharmaceutical quality system (PQS) based on a life-cycle approach as defined in WHO good manufacturing practices for pharmaceutical products: main principles (2). This approach facilitates innovation and continual improvement, and also strengthens the link between pharmaceutical development and manufacturing activities.

QRM principles should be used to develop the control strategy across all manufacturing and control stages – including materials sourcing and storage, personnel and materials flow, manufacture and packaging, quality control, quality assurance, storage and distribution activities, as described in relevant WHO guidelines (14) and other documents (22). Due to the inherent variability of biological processes and starting materials, ongoing trend analysis and periodic review are particularly important

elements of PQS. Thus, special attention should be paid to starting material controls, change control, trend analysis and deviation management in order to ensure production consistency. Monitoring systems should be designed so as to provide early detection of any unwanted or unanticipated factors that may affect the quality, safety and efficacy of the product. The effectiveness of the control strategy in monitoring, reducing and managing such risks should be regularly reviewed and the systems updated as required taking into account scientific and technical progress.

6. Personnel

- 6.1 Personnel responsible for production and control should have an adequate background in relevant scientific disciplines such as microbiology, biology, biometry, chemistry, medicine, pharmacy, pharmacology, virology, immunology, biotechnology and veterinary medicine, together with sufficient practical experience to enable them to perform their duties.
- 6.2 The health status of personnel should be taken into consideration as part of ensuring product safety. Where necessary, personnel engaged in production, maintenance, testing and animal care (and inspections) should be vaccinated with appropriate specific vaccines and have regular health checks. Any changes in the health status of personnel which could adversely affect the quality of the product should preclude their working in the production area, and appropriate records kept. The scope and frequency of health monitoring should be commensurate with the risk to the product and personnel.
- 6.3 Training in cleaning and disinfection procedures, hygiene and microbiology should emphasize the risk of microbial and adventitious contamination and the nature of the target microorganisms and growth media routinely used.
- 6.4 Where required to minimize the opportunity for cross-contamination, restrictions on the movement of all personnel (including quality control, maintenance and cleaning staff) should be defined on the basis of QRM principles. In general, all personnel including those not routinely involved in the production operation (such as management, engineering staff and validation staff or auditors) should not pass from areas with exposure to live microorganisms, genetically modified microorganisms, animal tissue, toxins, venoms or animals to areas where other products (inactivated or sterile) or different organisms are handled. If such passage is unavoidable during a working day, then contamination control measures (for example, clearly defined decontamination measures such as a complete change of appropriate clothing and shoes, and showering if applicable) should be followed by all personnel visiting any such production area unless otherwise justified on the basis of QRM.

- 6.5 Because the risks are difficult to manage, personnel working in an animal facility should be restricted from entering production areas where potential risks of cross-contamination exist.
- 6.6 Staff assigned to the production of BCG products should not work with other infectious agents. In particular, they should not work with virulent strains of *Mycobacterium tuberculosis*, nor should they be exposed to a known risk of tuberculosis infection (23). Additionally, they should be carefully monitored, with regular health checks that screen for tuberculosis infection.
- 6.7 If personnel working in BCG manufacturing and in animal quarters need to be reassigned to other manufacturing units they should not be allowed into such units until they pass their health check.

7. Starting materials

- 7.1 The source, origin and suitability of active substances, starting materials (for example, cryo-protectants and feeder cells), buffers and media (for example, reagents, growth media, serum, enzymes, cytokines, growth factors and amino acids) and other components of the finished product should be clearly defined and controlled according to the principles set out in WHO guidance on GMP for pharmaceutical products (2).
- 7.2 Manufacturers should retain information describing the source and quality of the biological materials used for at least 1 year after the expiry date of the finished products and according to local regulations concerning biological products. It has been found that documents retained for longer periods may provide useful information related to adverse events following immunization (AEFIs) and other investigations.
- 7.3 All starting material suppliers (that is, manufacturers) should be initially qualified on the basis of documented criteria and a risk-based approach. Regular assessments of their status should also be carried out. Particular attention should be given to the identification and monitoring of any variability that may affect biological processes. When starting materials are sourced from brokers who could increase the risk of contamination by performing repackaging operations under GMP (2, 4) they should be carefully qualified; an audit may form part of such qualification, as needed.
- 7.4 An identity test, or equivalent, should be performed on each batch of received starting materials prior to release. The number of containers sampled should be justified on the basis of QRM principles and in agreement with all applicable guidelines (2). The identification of all starting materials should be in compliance

with the requirements appropriate to the stage of manufacture. The level of testing should be commensurate with the qualification level of the supplier and the nature of the materials used. In the case of starting material used to manufacture active substances the number of samples taken should be based on statistically recognized criteria and QRM principles (2). However, for starting materials and intermediates used in the formulation of finished product each container should be sampled for identity testing in accordance with the main principles of GMP for pharmaceutical products unless reduced testing has been validated.

- 7.5 The sampling process should not adversely affect the quality of the product. Incoming starting materials should be sampled under appropriate conditions in order to prevent contamination and cross-contamination.
- 7.6 Where justified (such as the special case of sterile starting materials) it may be acceptable to reduce the risk of contamination by not performing sampling at the time of receipt but to perform the testing later on samples taken at the time of use. In such cases, release of the finished product is conditional upon satisfactory results of these tests.
- 7.7 Where the necessary tests for approving starting materials take a significantly long time, it may be permissible by exception to process starting materials before the test results are available. The use of these materials should be clearly justified in a documented manner, and the risks should be understood and assessed under the principles of QRM. In such cases, release of the finished product is conditional upon satisfactory results from the tests. It must be ensured that this is not standard practice and occurs only with justification of the risk taken.
- 7.8 The risk of contamination of starting materials during their passage along the supply chain should be assessed, with particular emphasis on adventitious agents such as those causing TSEs (24). Other materials that come into direct contact with manufacturing equipment and/or with potential product contact surfaces (such as filter media, growth media during aseptic process simulations and lubricants) should also be controlled. A quality risk assessment should be performed to evaluate the potential for adventitious agents in biological starting materials.
- 7.9 Where required, the sterilization of starting materials should be carried out by heat whenever possible. Where necessary, other appropriate validated methods may also be used for this purpose (such as irradiation and filtration).
- 7.10 The controls required for ensuring the quality of sterile starting materials and of the aseptic manufacturing process should be based on the principles and guidance contained in the current WHO good manufacturing practices for sterile pharmaceutical products (3).

- 7.11 The transport of critical materials, reference materials, active substances, human tissues and cells to the manufacturing site should be controlled as part of a written quality agreement between the responsible parties if they are different commercial entities. Manufacturing sites should have documentary evidence of adherence to the specified storage and transport conditions, including cold chain requirements, if required. The required traceability – starting at tissue establishments through to the recipient(s), and including the traceability of materials in contact with the cells or tissues – should be ensured, maintained and documented.

8. Seed lots and cell banks

- 8.1 The recommendations set out in WHO good manufacturing practices for active pharmaceutical ingredients (4) should be followed – specifically section 18 on specific guidance for active pharmaceutical ingredients manufactured by cell culture/fermentation.
- 8.2 Where human or animal cells are used as feeder cells in the manufacturing process, appropriate controls over their sourcing, testing, transport and storage should be in place.
- 8.3 In order to prevent the unwanted drift of genetic properties which might result from repeated subcultures or multiple generations, the production of biological products obtained by microbial culture, cell culture or propagation in embryos and animals should be based on a system of master and working seed lots and/or cell banks; which is the beginning of the manufacturing process of certain biological products (for example, vaccines).
- 8.4 The number of generations (expressed as passages or doublings) between the seed lot or cell bank and the finished product, defined as maximum, should be consistent with the marketing authorization dossier and should not be exceeded.
- 8.5 Cell-based medicinal products are often generated from a cell stock obtained from a limited number of passages. In contrast with the two-tier system of MCBs and WCBs, the number of production runs from a cell stock is limited by the number of aliquots obtained after expansion and does not cover the entire life-cycle of the product. Cell stock changes should be covered by a validation protocol and communicated to the NRA, as applicable.
- 8.6 Establishment and handling of the MCBs and WCBs should be performed under conditions which are demonstrably appropriate. These should include an appropriately controlled environment to protect the seed lot and the cell bank, and the personnel handling them. To establish the minimum requirements for clean

room grade and environmental monitoring in the case of vaccines see the WHO *Environmental monitoring of clean rooms in vaccine manufacturing facilities: points to consider for manufacturers of human vaccines* (25). During the establishment of the seed lot and cell bank, no other living or infectious material (such as viruses, cell lines or microbial strains) should be handled simultaneously in the same area or by the same persons, as set out in current WHO Recommendations (26).

- 8.7 Quarantine and release procedures for master and working cell banks/seed lots should be followed, including adequate characterization and testing for contaminants. Initially, full characterization testing of the MCB should be done, including genetic identification. A new MCB (from a previous initial clone, MCB or WCB) should be subjected to the same established testing as the original MCB, unless otherwise justified. Thereafter, the viability, purity and other stability-indicating attributes of seed lots and cell banks should be checked regularly according to justified criteria. Evidence of the stability and recovery of the seed lots and banks should be documented and records should be kept in a manner that permits trend evaluation.
- 8.8 Each storage container should be adequately sealed, clearly labelled and kept at an appropriate temperature. A stock inventory should be kept. The storage temperature should be recorded continuously and, where applicable, the liquid nitrogen level should be monitored. Any deviation from the set limits, and any corrective and preventive action taken, should be recorded. Temperature deviations should be detected as early as possible (for example, through the use of an alarm system for temperature and nitrogen levels).
- 8.9 Seed lots and cell banks should be stored and used in such a way as to minimize the risks of contamination or alteration (for example, stored in qualified ultra-low temperature freezers or liquid nitrogen storage containers). Control measures for the storage of different seeds and/or cells in the same area or equipment should prevent mix-up and should take into account the infectious nature of the materials in order to prevent cross-contamination.
- 8.10 MSLs, MCBs, and preferably also WSLs and WCBs, should be stored in two or more controlled separate sites in order to minimize the risk of total loss due to natural disaster, equipment malfunction or human error. A contingency plan should be in place.
- 8.11 The storage and handling conditions for the cell or seed banks should be defined. Access should be controlled and restricted to authorized personnel, and appropriate access records maintained. Records of location, identity and inventory of individual containers should also be kept. Once containers are removed from the seed lot/cell bank management system they should not be returned to stock.

9. Premises and equipment

- 9.1 In general, preparations containing live microorganisms or live viruses should not be manufactured and containers should not be filled in areas used for the processing of other pharmaceutical products. However, if the manufacturer can demonstrate and validate effective containment and decontamination of the live microorganisms and viruses then the use of multi-product facilities may be justifiable. In such cases, measures such as campaign production, closed systems and/or disposable systems should be considered and should be based on QRM principles (see sections 10 and 13 below on containment and campaign production respectively).
- 9.2 Documented QRM should be carried out for every additional product in a biological manufacturing multi-product facility, which may include a potency and toxicological evaluation based on cross-contamination risks. Other factors to be taken into account include facility/equipment design and use, personnel and material flows, microbiological controls, physicochemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the relevant limits established from product evaluation. The outcome of the QRM process should be the basis for determining the necessity for premises and equipment to be dedicated to a particular product or product family, and the extent to which this should be the case. This may include dedicating specific product-contact parts. The NRA should approve the use of a manufacturing facility for the production of multiple products on case-to-case basis.
- 9.3 Killed vaccines, antisera and other biological products – including those made by rDNA techniques, toxoids and bacterial extracts – may, following inactivation, be manufactured on the same premises provided that adequate decontamination and cleaning measures are implemented on the basis of QRM.
- 9.4 Cleaning and sanitization should take into account the fact that processes often include the handling of growth media and other growth-promoting agents. Validation studies should be carried out to ensure the effectiveness of cleaning, sanitization and disinfection, including elimination of residues of used agents. Environmental and personnel safety precautions should be taken during the cleaning and sanitization processes. The use of cleaning and sanitizing agents should not pose any major risk to the performance of equipment.

The use of closed systems to improve asepsis and containment should be considered where practicable. Where open systems are utilized during processing (for example, during addition of growth supplements, media, buffers and gases, and during sampling and aseptic manipulations during the handling of live cells such as in cell-therapy products) control measures should be put in place to prevent

contamination, mix-up and cross-contamination. Logical and unidirectional flows of personnel, materials and processes, and the use of clean-in-place and sterilize-in-place systems, should be considered wherever possible. Where sterile single-use systems such as bags and connectors are utilized, they should be qualified with respect to suitability, extractables, leachables and integrity.

- 9.5 Because of the variability of biological products, and of the corresponding manufacturing processes, approved starting materials that have to be measured or weighed for the production process (such as growth media, solutions and buffers) may be kept in small stocks in the production area for a specified period of time according to defined criteria – such as for the duration of manufacture of the batch or of the campaign. Appropriate storage conditions and controls should be maintained during such temporary storage. These materials should not be returned to the general stock. Materials used to formulate buffers, growth media and so on should be weighed and made into a solution in a contained area using local protection (such as a classified weighing booth) and outside the aseptic processing areas in order to minimize particulate contamination of the latter.
- 9.6 In manufacturing facilities, the mix-up of entry and exit of personnel should be avoided through the use of separate changing rooms or through procedural controls where Biosafety Risk Group 3 or 4 organisms are handled (20).

10. Containment

- 10.1 Airborne dissemination of live microorganisms and viruses used for the production process, including those from personnel, should be avoided.
- 10.2 Adequate precautions should be taken to avoid contamination of the drainage system with dangerous effluents. Drainage systems should be designed in such a way that effluents can be effectively neutralized or decontaminated to minimize the risk of cross-contamination. Specific and validated decontamination systems should be considered for effluents when infectious and/or potentially infectious materials are used for production. Local regulations should be complied with in order to minimize the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials.
- 10.3 Dedicated production areas should be used for the handling of live cells capable of persistence in the manufacturing environment, for pathogenic organisms of Biosafety Risk Group 3 or 4 and/or for spore-forming organisms until the inactivation process is accomplished and verified. For *Bacillus anthracis*, *Clostridium tetani* and *Clostridium botulinum* strictly dedicated facilities should be utilized for each individual product. Up-to-date information on these and other

high-risk or “special” agents should be sought from major information resources (27). Where campaign manufacture of spore-forming organisms occurs in a facility or suite of facilities only one product should be processed at any one time.

Use of any pathogenic organism above Biosafety Risk Group 3 may be permitted by the NRA according to the biohazard classification of the organism, the risk assessment of the biological product and its emergency demand.

- 10.4 Production of BCG-related product should take place in a dedicated area and by means of dedicated equipment and utilities (such as heating, ventilation and air conditioning (HVAC) systems) in order to minimize the hazard of cross-contamination.
- 10.5 Specific containment requirements apply to poliomyelitis vaccine in accordance with the WHO global action plan to minimize poliovirus facility-associated risk (28) and with WHO Guidelines for the safe production and quality control of inactivated poliomyelitis vaccine manufactured from wild polioviruses (29). The measures and procedures necessary for containment (that is, for protecting the environment and ensuring the safety of the operator) should not conflict with those for ensuring product quality.
- 10.6 Air-handling systems should be designed, constructed and maintained to minimize the risk of cross-contamination between different manufacturing areas as required. The need for dedicated air-handling units or single-pass systems should be based on QRM principles, taking into account the biohazard classification and containment requirements of the relevant organism, and process and equipment risks. In the case of Biosafety Risk Group 3 organisms, air should not be recirculated to any other area in the facility and should be exhausted through high-efficiency particulate air (HEPA) filters that are regularly checked for performance. A dedicated non-recirculating ventilation system and HEPA-filtering of exhaust air are required when handling Biosafety Risk Group 4 organisms (27).
- 10.7 Primary containment equipment should be designed and initially qualified for integrity in order to ensure that the escape of biological agents and/or material into the immediate working area and outside environment is prevented. Thereafter, in line with relevant guidelines and QRM principles, periodical tests should be performed to ensure that the equipment is in proper working condition.
- 10.8 Activities associated with the handling of live biological agents (such as centrifugation and blending of products which can lead to aerosol formation) should be contained in such a way as to prevent contamination of other products or the egress of live agents into the working and/or outside environment. The viability of such organisms and their biohazard classification should be taken into consideration as part of the management of such risks.

Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Validated decontamination measures should be available for each organism or groups of related organisms. Where different strains of a single bacteria species or very similar viruses are involved, the decontamination process may be validated with one representative strain, unless the strains vary significantly in their resistance to the decontaminating agent(s) used.

- 10.9 Areas where Biosafety Risk Group 3 or 4 organisms are handled should always have a negative air pressure relative to the environment. This will ensure the containment of the organism in unlikely events such as failure of the door interlock. Air-lock doors should be interlocked to prevent them being opened simultaneously. Differential pressure alarms should be present wherever required, and should be validated and monitored.
- 10.10 Air-vent filters should be hydrophobic and subject to integrity testing at intervals determined by a QRM approach.
- 10.11 Where the filtration of exhaust air is necessary, the safe changing of filters should be ensured or bag-in-bag-out housings should be employed. Once removed, filters should be decontaminated and properly destroyed. In addition to HEPA filtration other inactivation technologies such as heat inactivation and steam scavenging may be considered for exhaust air to ensure effective inactivation of pathogenic organisms of Biosafety Risk Group 3 and/or 4.

11. Clean rooms

- 11.1 The WHO good manufacturing practices for sterile pharmaceutical products (3) defines and establishes the required class/grade of clean areas for the manufacture of sterile products according to the operations performed, including final aseptic fill. Additionally, in order to address the specific manufacturing processes involved in the production of biological products, and particularly vaccines, the WHO *Environmental monitoring of clean rooms in vaccine manufacturing facilities: points to consider for manufacturers of human vaccines* (25) guidance document may be used to develop the environmental classification requirements for biological manufacturing processes.

As part of the control strategy, the degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the intermediate or finished product, and also to the production step, taking into account the potential level of contamination of the starting materials and the risks to the finished product.

11.2 The environmental monitoring programme should be supplemented with methods to detect the presence of the specific microorganisms used for production (for example, recombinant yeast and toxin- or polysaccharide-producing bacteria). The environmental monitoring programme may also include detection of the produced organisms and adventitious agents of production organisms, especially when campaign manufacture is applied on the basis of QRM principles.

12. Production

12.1 Since cultivation conditions, media and reagents are designed to promote the growth of cells or microbial organisms, typically in an axenic state, particular attention should be paid to the control strategy for ensuring that effective steps are in place for preventing or minimizing the occurrence of unwanted bioburden, endotoxins, viruses of animal and human origin, and associated metabolites.

12.2 The QRM process should be the basis for implementing the technical and organizational measures required to control the risks of contamination and cross-contamination. These could include, though are not limited to:

- carrying out processing and filling in segregated areas;
- containing material transfer by means of an airlock and appropriate type of pass box with validated transfer procedures, clothing change and effective washing and decontamination of equipment;
- recirculation of only treated (HEPA-filtered) air;
- acquiring knowledge of the key characteristics (for example, pathogenicity, detectability, persistence and susceptibility to inactivation) of all cells, organisms and any adventitious agents within the same facility;
- when considering the acceptability of concurrent work in cases where production is characterized by multiple small batches from different starting materials (for example, cell-based products) taking into account factors such as the health status of donors and the risk of total loss of a product from or for specific patients during development of the cross-contamination control strategy;
- preventing the risk of live organisms and spores entering non-related areas or equipment by addressing all potential routes of cross-contamination (for example, through the HVAC system) through the use of single-use components and closed systems;
- conducting environmental monitoring specific to the microorganism being manufactured in adjacent areas while paying attention to cross-contamination risks arising from the use of certain monitoring equipment

- (such as that used for airborne particle monitoring) in areas handling live and/or spore-forming organisms;
- using campaign-based production (see section 13 below).
- 12.3 When applicable, the inoculum preparation area should be designed so as to effectively control the risk of contamination, and should be equipped with a biosafety hood for primary containment.
- 12.4 If possible, growth media should be sterilized *in situ* by heat or in-line microbial-retentive filters. Additionally, in-line microbial-retentive filters should be used for the routine addition of gases, media, acids, alkalis and so on to fermenters or bioreactors.
- 12.5 Data from continuous monitoring of certain production processes (such as fermentation) should form part of the batch record. Where continuous culture is used, special consideration should be given to parameters such as temperature, pH, pO₂, CO₂ and the rate of feed or carbon source with respect to growth of cells.
- 12.6 In cases where a viral inactivation or removal process is performed, measures should be taken (for example, in relation to facility layout, unidirectional flow and equipment) to avoid the risk of recontamination of treated products by non-treated products.
- 12.7 A wide variety of equipment and components (for example, resins, matrices and cassettes) are used for purification purposes. QRM principles should be applied to devise the control strategy regarding such equipment and associated components when used in campaign manufacture and in multi-product facilities. The reuse of components at different stages of processing of one product is discouraged but, if performed, should be validated. Acceptance criteria, operating conditions, regeneration methods, lifespan and sanitization or sterilization methods, cleaning process, and hold time between the use of reused components should be defined and validated. The reuse of components for different products is not acceptable.
- 12.8 Where adverse donor (human or animal) health information becomes available after procurement and/or processing, and this information relates to product quality, then appropriate measures should be taken – including product recall, if applicable.
- 12.9 Antibiotics may be used during the early stages of production to help prevent inadvertent microbial contamination or to reduce the bioburden of living tissues and cells. In this case, the use of antibiotics should be well justified, and they should be cleared from the manufacturing process at the stage specified in the marketing authorization. Acceptable residual levels should be defined and validated. Penicillin and other beta-lactam antibiotics should not be used at any stage of the process.

12.10 A procedure should be in place to address equipment and/or accessories failure (such as air vent filter failure) which should include a product impact review. If such failures are discovered following batch release the NRA should be notified and the need for a batch recall should be considered.

13. Campaign production

- 13.1 The decision to use a facility or filling line for campaign manufacture should be justified in a documented manner and should be based on a systematic risk approach for each product (or strain) taking into account the containment requirements and the risk of cross-contamination to the next product. Campaign changeover procedures, including sensitive techniques used for the determination of residues, should be validated and proper cleaning acceptance criteria should be defined on a toxicology basis of product residues from the last campaign, as applicable. Equipment assigned to continued production or to campaign production of successive batches of the same intermediate product should be cleaned at appropriate validated intervals to prevent build-up and carry-over of contaminants (such as product degradants or objectionable levels of microorganisms).
- 13.2 For downstream operations of certain products (for example, pertussis or diphtheria vaccines) campaign production may be acceptable if well justified. For finishing operations (formulation and filling) the need for dedicated facilities or the use of campaigns in the same facility will depend on the specific characteristics of the biological product, on the characteristics of the other products (including any non-biological products), on the filling technologies used (such as single-use closed systems) and on local NRA regulations. Labelling and packaging operations can be carried out in a multi-product facility.
- 13.3 Campaign changeover involves intensive decontamination/sterilization (if required) and cleaning of the equipment and manufacturing area. Decontamination/sterilization (if required) and cleaning should include all equipment and accessories used during production, as well as the facility itself. The following recommendations should be considered:
- waste should be removed from the manufacturing area or sent to the bio-waste system in a safe manner;
 - materials should be transferred by a validated procedure;
 - the Quality Unit should confirm area clearance by inspection, and review the campaign changeover data (including monitoring results) prior to releasing the area for the next product.

- 13.4 When required, the corresponding diluent for the product can be filled in the same facility in line with the defined campaign production strategy for finished product.
- 13.5 When campaign-based manufacturing is considered, the facility layout and the design of the premises and equipment should permit effective cleaning and decontamination/sterilization (if required) based on QRM principles and validated procedures following the production campaign. In addition, consideration may need to be given at the design stage of facility layout to the possible need for fumigation.

14. Labelling

- 14.1 The information provided on the inner label (also called the container label) and on the outer label (on the packaging) should be readable and legible, and the content approved by the NRA.
- 14.2 Minimal key information should be printed on the inner label, and additional information should be provided on the outer label (for example, carton) and/or product leaflet.
- 14.3 The suitability of labels for low and ultra-low storage temperatures should be verified, if applicable. The label should remain properly attached to the container under different storage conditions during the shelf-life of the product. The label and its adhesive should have no adverse effect on the quality of the product caused by leaching, migration and/or other means.

15. Validation

- 15.1 Biological processes, handling of live materials and using campaign-based production, if applicable, are the major aspects of biological product manufacturing which require process and cleaning validation. The validation of such processes – given the typical variability of biological products, the possible use of harmful and toxic materials and the need for inactivation processes – plays an important role in demonstrating production consistency and in proving that the critical process parameters and product attributes are controlled. Where available, WHO guidance documents should be consulted on the validation of specific manufacturing methods (for example, virus removal or inactivation (21)).
- 15.2 A QRM approach should be used to determine the scope and extent of validation.
- 15.3 All critical biological processes (including inoculation, multiplication, fermentation, cell disruption, inactivation, purification, virus removal, removal of toxic and harmful additives, filtration, formulation and aseptic filling) are

subject, as applicable, to process validation. Manufacturing control parameters to be validated may include specific addition sequences, mixing speeds, time and temperature controls, limits of light exposure and containment.

- 15.4 After initial process validation studies have been finalized and routine production has begun, critical processes should be subject to monitoring and trending with the objective of assuring consistency and detecting any unexpected variability. The monitoring strategy should be defined, taking into consideration factors such as the inherent variability, complexity of quality attributes and heterogeneity of biological products. A system or systems for detecting unplanned departures from the process as designed should be in place to ensure that the process remains in a state of control. Collection and evaluation of information and data on the performance of the process will allow for detection of undesired process variability and will determine whether action should be taken to prevent, anticipate and/or correct problems so that the process remains under control.
- 15.5 Cleaning validation should be performed in order to confirm the effectiveness of cleaning procedures designed to remove biological substances, growth media, process reagents, cleaning agents, inactivation agents and so on. Careful consideration should be given to cleaning validation when campaign-based production is practised.
- 15.6 Critical processes for inactivation or elimination of potentially harmful microorganisms of Biosafety Risk Group 2 or above, including genetically modified ones, are subject to validation.
- 15.7 Process revalidation may be triggered by a process change as part of the change-control system. In addition, because of the variability of processes, products and methods, process revalidation may be conducted at predetermined regular intervals according to risk considerations. A detailed review of all changes, trends and deviations occurring within a defined time period – for example, 1 year, based on the regular product quality review (PQR) – may indicate a need for process revalidation.
- 15.8 The integrity and specified hold times of containers used to store intermediate products should be validated unless such intermediate products are freshly prepared and used immediately.

16. Quality control

- 16.1 As part of quality control sampling and testing procedures for biological materials and products, special consideration should be given to the nature of the materials being sampled (for example, the need to avoid contamination, ensure

biocontainment and/or cold chain requirements) in order to ensure that the testing carried out is representative.

- 16.2 Samples for post-release use typically fall into one of two categories – reference samples or retention samples – for the purposes of analytical testing and identification respectively. For finished products the reference and retention samples will in many instances be presented identically as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable.

Reference samples of biological starting materials should be retained under the recommended storage conditions for at least 1 year beyond the expiry date of the corresponding finished product. Reference samples of other starting materials (other than solvents, gases and water) as well as intermediates for which critical parameters cannot be tested in the final product should be retained for at least 2 years after the release of the product if their stability allows for this storage period. Certain starting materials such as components of growth media need not necessarily be retained.

Retention samples of a finished product should be stored in their final packaging at the recommended storage conditions for at least 1 year after the expiry date.

- 16.3 For cell-based products, microbiological tests (for example, sterility tests or purity checks) should be conducted on cultures of cells or cell banks free of antibiotics and other inhibitory substances in order to provide evidence of the absence of bacterial and fungal contamination, and to be able to detect fastidious organisms where appropriate. Where antibiotics are used, they should be removed by filtration at the time of testing.
- 16.4 The traceability, proper use and storage of reference standards should be ensured, defined and recorded. The stability of reference standards should be monitored, and their performance trended. The WHO Recommendations for the preparation, characterization and establishment of international and other biological reference standards (30) should be followed.
- 16.5 All stability studies – including real-time/real-condition stability, accelerated stability and stress testing – should be carried out according to relevant WHO and other guidelines (31) or other recognized documents. Trend analysis of the test results from the stability monitoring programme should assure the early detection of any process or assay drift, and this information should be part of the PQR of biological products.
- 16.6 For products where ongoing stability monitoring would normally require testing using animals, and no appropriate alternative or validated techniques are available,

the frequency of testing may take into account a risk-based approach. The principle of bracketing and matrix designs may be applied if scientifically justified in the stability protocol.

- 16.7 All analytical methods used in the quality control and in-process control of biological products should be well characterized, validated and documented to a satisfactory standard in order to yield reliable results. The fundamental parameters of this validation include linearity, accuracy, precision, selectivity/specificity, sensitivity and reproducibility (32–35).
- 16.8 For test methods described in relevant pharmacopoeial monographs, qualification of the laboratory test equipment and personnel should be performed. In addition, repeat precision and comparability precision should be shown in the case of animal tests. Repeatability and reproducibility should also be demonstrated by reviewing retrospective test data.

In addition to the common parameters typically used for validating assays (such as accuracy and precision) additional measurements (for example, of the performance of references, critical reagents and/or cell lines) should be considered during the validation of bioassays based on the biological nature of the assay and reagents used.

17. Documentation (batch processing records)

- 17.1 In general, the processing records of regular production batches should provide a complete account of the manufacturing activities of each batch of biological product showing that it has been produced, tested and dispensed into containers in accordance with the approved procedures.

In the case of vaccines, a batch processing record and a summary protocol should be prepared for each batch for the purpose of lot release by the NRA. The information included in the summary protocol should follow the WHO Guidelines for independent lot release of vaccines by regulatory authorities (36). The summary protocol and all associated records should be of a type approved by the NRA.

- 17.2 Manufacturing batch records should be retained for at least 1 year after the expiry date of the batch of the biological product and should be readily retrievable for inspection by the NRA. It has been found that documents retained for longer periods may provide useful information related to AEFI and other investigations.
- 17.3 Starting materials may require additional documentation on source, origin, supply chain, method of manufacture and controls applied in order to ensure an appropriate level of control, including of microbiological quality if applicable.

- 17.4 Some product types may require a specific definition of what materials constitute a batch – particularly somatic cells in the context of ATMPs. For autologous and donor-matched situations, the manufactured product should be viewed as a batch.

18. Use of animals

- 18.1 A wide range of animals is used for the manufacture or quality control of biological products. Special considerations are required when animal facilities are present at a manufacturing site.
- 18.2 The presence of live animals in the production area should be avoided unless otherwise justified. Embryonated eggs are allowed in the production area, if applicable. If the extraction of tissues or organs from animals is required then particular care should be taken to prevent contamination of the production area (for example, appropriate disinfection procedures should be undertaken).
- 18.3 Areas used for performing tests involving animals or microorganisms should be well separated from premises used for the manufacturing of products and should have completely separate ventilation systems and separate staff. The separation of different animal species before and during testing should be considered, as should the necessary animal acclimatization process, as part of the test requirements.
- 18.4 In addition to monitoring compliance with TSE regulations (24) other adventitious agents that are of concern (including those causing zoonotic diseases and diseases in source animals) should also be monitored and recorded in line with specialist advice on establishing such programmes. Instances of ill health occurring in the source/donor animals should be investigated with respect to their suitability, and the suitability of in-contact animals, for continued use (for example, in manufacture, as sources of starting materials, and for quality control and safety testing). Decisions should be documented.
- 18.5 A look-back procedure should be in place in relation to the decision-making process used to evaluate the continued suitability of the biological active substance or finished product in which animal-sourced starting materials have been used or incorporated. This decision-making process may include the retesting of reference samples from previous collections from the same donor animal (where applicable) to establish the last negative donation. The withdrawal period of therapeutic agents used to treat source/donor animals should be documented and should be taken into account when considering the removal of those animals from the programme for defined periods.

- 18.6 Particular care should be taken to prevent and monitor infections in source/donor animals. Measures taken should cover aspects such as sourcing, facilities, husbandry, biosafety procedures, testing regimes, control of bedding and feed materials, 100% fresh air supply, appropriate design of the HVAC system, water supply and appropriate temperature and humidity conditions for the species being handled. This is of special relevance to SPF animals where pharmacopoeial monograph requirements should be met. Housing and health monitoring should also be defined for other categories of animals (for example, healthy flocks or herds).
- 18.7 For products manufactured from transgenic animals, traceability should be maintained in the creation of such animals from the source animals. Note should be taken of national requirements for animal quarters, care and quarantine.
- 18.8 For different animal species and lines, key criteria should be defined, monitored and recorded. These may include the age, sex, weight and health status of the animals.
- 18.9 Animals, biological agents and tests carried out should be appropriately identified to prevent any risk of mix-up and to control all identified hazards.
- 18.10 The facility layout should ensure a unidirectional and segregated flow of healthy animals, inoculated animals and waste-decontamination areas. Personnel and visitors should also follow a defined flow in order to avoid cross-contamination.

19. Authors and acknowledgements

The scientific basis for the revision of these WHO Guidelines was discussed at a working group meeting held in Bangkok, Thailand, 10–13 September 2007 and attended by: Dr M.M.F. Ahmed, Center for Control of Biologicals and Vaccines, Egypt; Dr H. Alitamsar, PT Bio Farma, Indonesia; Mr P. Angtrakool, Ministry of Public Health, Thailand; Dr D. Buckley, Consultant, Monash, Australia; Dr M. Dennehy, The Biovac Institute, South Africa; Ms X. Dong, Beijing Tiantan Biological Products Co. Ltd, China; Dr H.J.M. van de Donk, Consultant, Den Haag, Netherlands; Dr M. Gheisarzardeh, Ministry of Health and Medical Education, the Islamic Republic of Iran; Dr H.T. Hong, National Institute for Control of Vaccine and Biologicals, Viet Nam; Mrs W. Jariyapan, WHO Regional Office for South-East Asia, India; Mr M. Javadekar, Serum Institute of India Ltd, India; Dr D. Jiang, State Food and Drug Administration, China; Mrs T. Jivapaisarnpong, Ministry of Public Health, Thailand; Dr A. Khadem, Pasteur Institute of Iran, the Islamic Republic of Iran; Professor S. Khomvilai, Thai Red Cross Society, Thailand; Dr K-H. Kim, Korean Food and Drug Administration, Republic of Korea; Dr Kustantinah, National Agency of Drug and Food Control, Indonesia; Professor C.K. Lee, Advisor to the Korean

Food and Drug Administration, Republic of Korea; Mrs J. Li, Sinovac Biotech Co. Ltd, China; V.G. Maqueda, Biologist, Buenos Aires, Argentina; Dr K-I. Min, Korean Food and Drug Administration, Republic of Korea; Mr I. Rees, Medicines and Healthcare Products Regulatory Agency, the United Kingdom; Dr C.H. Sia, Health Sciences Authority, Singapore; Dr M. Suhardono, PT Bio Farma, Indonesia; Ms J. Teo, Centre for Drug Administration, Singapore; Ms P.S. Thanaphollert, Ministry of Public Health, Thailand; Mr S. Thirapakpoomanunt, Ministry of Public Health, Thailand; Ms A.R.T. Utami, National Agency of Drug and Food Control, Indonesia; Dr D.T.H. Van, Institute for Vaccine and Biologicals, Viet Nam; Mr B. Wibisono, National Agency of Drug and Food Control, Indonesia; Mr J. Yang, Kunming Institute of Medical Biology, China; Mr Y. Yu, Kunming Institute of Medical Biology, China; and Dr I. Knezevic and Dr S. Lambert, World Health Organization, Switzerland – and a WHO drafting group meeting held in Geneva, Switzerland, 30–31 October 2013 and attended by: Mr R. Acs, Central Drugs Standard Control Organisation, India; Mr M. Eisenhawer, WHO Regional Office for South-East Asia, India; Dr S. Fakhrzadeh, Ministry of Health and Medical Education, the Islamic Republic of Iran; V.G. Maqueda, Biologist, Buenos Aires, Argentina; Mrs K. Porkaew, Ministry of Public Health, Thailand; Dr S.O. Rumiano, Consultant, Buenos Aires, Argentina; Dr Y. Wang, National Institutes for Food and Drug Control, China; Mr B. Wibisono, National Agency of Drug and Food Control, Indonesia; and Dr A. Chawla, Dr A.R. Khadem, Dr I. Knezevic, Dr S. Kopp and Dr D. Lei, World Health Organization, Switzerland.

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Switzerland following a consultation held in Tunis, Tunisia, 22–24 July 2014 and attended by: Dr H. Baiao, National Authority for Medicines and Health Products, Portugal; Mrs R. Bose, Ministry of Health and Family Welfare, India; Mr C. Cabral, Butantan Institute, Brazil; Dr R. Chaplinsky, GSK Vaccines, Belgium; Dr A. Chawla, Consultant, Greater Noida, India; Mr M. Diagne, Direction de la Pharmacie et des Laboratoires, Senegal; Mr M. Eisenhawer, WHO Regional Office for South-East Asia, India; Dr S. Fakhrzadeh, Ministry of Health and Medical Education, the Islamic Republic of Iran; Mrs R. Friksa, Directorate of Pharmacy Inspection, Tunisia; Dr M. Gershman, Pfizer, the USA; Ms A.R. Cornelio Geyer, Agência Nacional de Vigilância Sanitária, Brazil; Dr E. Griffiths, Consultant, Kingston-upon-Thames, the United Kingdom; Dr N. Harjee, Consultant, Ontario, Canada; Ms D.T.M. Hang, Ministry of Health, Viet Nam; Dr H. Langar, WHO Regional Office for the Eastern Mediterranean, Egypt; Dr P. Lauer, Sanofi Pasteur, France; Dr C.K. Lee, Korea Food and Drug Administration, Republic of Korea; Dr H. Leng, Medicines Regulatory Authority, South Africa; Dr M.G. Lopez Santos, Comisión Federal para la Protección contra Riesgos Sanitarios, Mexico; V.G. Maqueda, Biologist, Buenos Aires, Argentina; Dr A. Mihaylova, Bulgarian Drug Agency, Bulgaria; Dr J. Miteva, Bulgarian Drug Agency, Bulgaria; Dr S. Pagliusi, DCVMN International, Switzerland; Dr V.A. Pessanha, Oswaldo Cruz Foundation, Brazil; Mrs K. Porkaew, Ministry of Public Health, Thailand; Dr S. Ramanan, Amgen, the USA; Dr P. Rampignon, GSK Vaccines, Belgium; Dr D. Rebeski, The Biovac Institute, South Africa; Dr M. Refaat, Central Administration for Pharmaceutical Affairs, Egypt; Dr S.O. Rumiano, Consultant, Buenos Aires, Argentina; Dr A.L. Salvati, Agenzia Italiana del Farmaco, Italy; Dr J. Shin, WHO Regional Office for the Western Pacific, Philippines; Dr W. Stevens, Health Canada, Canada; Dr I. Susanti, PT Bio Farma, Indonesia; Ms C.S. Takata, Butantan Institute, Brazil; Dr S. Uddin, Directorate General of Drug Administration, Bangladesh; Dr Y. Wang, National Institutes for Food and Drug Control, China; Mr B. Wibisono, National Agency of Drug and Food Control, Indonesia; and Dr A.K. Broojerdi, Dr D. Lei, Dr I. Streipa-Nauman and Dr D.J. Wood, World Health Organization, Switzerland.

The document WHO/BS/2015.2253, incorporating comments received from regulators and industry following public consultation on the WHO Biologicals website, was prepared by V.G. Maqueda, Biologist, Buenos Aires, Argentina; Dr B. Yáñez Chamizo, Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos, Cuba; Dr S. Fakhrzadeh, Ministry of Health and Medical Education, the Islamic Republic of Iran; Dr S.O. Rumiano, Consultant, Buenos Aires, Argentina; Dr Y. Wang, National Institutes for Food and Drug Control, China; Dr A. Chawla, Consultant, Greater Noida, India; Dr M. Refaat, Central Administration for Pharmaceutical Affairs, Egypt; Dr A. Khadem, Pasteur Institute of Iran, the Islamic Republic of Iran; and Dr M. Chafai, Dr D. Lei, Dr D. Mubangizi and Dr I.R. Thrussell, World Health Organization, Switzerland.

Further changes were subsequently made to document WHO/BS/2015.2253 by the WHO Expert Committee on Biological Standardization.

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3.3 WHO guidelines on good manufacturing practices for blood establishments

(jointly with the Expert Committee on Biological Standardization)

Annex 4, WHO Technical Report Series, 961,
2011

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1. Introduction

The World Health Organization (WHO) requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (1) define a quality assurance system based on (i) the existence of a national structure that is independent of manufacturers, (ii) compliance with the process of quality assurance for biological products — i.e. control of starting material(s), production processes and final product(s) — and (iii) strict adherence to the principles of good manufacturing practice (GMP). Since the last revision of these requirements in 1992, two relevant items have been reviewed and new recommendations adopted, namely on virus inactivation and removal of plasma derivatives (2004) (2) and human plasma for fractionation (2007) (3). However, a number of issues, such as the requirement for a quality assurance system in blood establishments, have not yet been addressed. The WHO Expert Committee on Biological Standardization (ECBS), therefore, considered that the development of WHO guidelines on GMP for blood establishments is of highest priority in assisting Member States to meet their needs in this area, as requested by the International Conference of Drug Regulatory Authorities in 2008 (4).

The importance of establishing reliable quality assurance systems for the whole chain of blood collection, processing and distribution of blood components in blood establishments was also emphasized by the Sixty- third World Health Assembly in resolution WHA63.12 on the availability, safety and quality of blood products (5). In that resolution, quality assurance was seen as a necessary measure that would contribute to increased global availability of plasma that meets internationally recognized standards.

Resolution WHA63.12 recognized that a special effort is needed to strengthen globally the technical capacity of national regulatory authorities (NRAs) to assure the appropriate control of blood products. The resolution recalls earlier related resolutions which urged Member States to promote the full implementation of well organized, nationally coordinated and sustainable blood programmes stressing the role of voluntary, non-remunerated blood donations from low-risk populations.

In recent years, safety and quality in the transfusion chain has become an important topic in many countries and regions (6). Blood establishments should establish and maintain quality systems, based on GMP principles, involving all activities that determine quality policy objectives and responsibilities, and should implement them by such means as quality planning, quality control, quality assurance and quality improvement. A GMP approach to manufacturing safe blood components that consistently meet predefined specifications and customers' expectations provides a model that allows for a documented system of incorporating quality into the entire process. When collecting and processing blood and plasma from human donors, GMP considerations should be addressed in a biological context due to the specific characteristics of materials of human origin.

The guidelines in this document include:

- general GMP topics such as quality management, personnel, documentation, premises and equipment, qualification and validation, materials management, contract manufacturing, and complaints and recalls;
- GMP concepts such as quality risk management and product quality reviews;
- topics specific to the manufacturing of blood components from donor selection to distribution of the final product.

They address current and widely accepted GMP principles that are relevant to the consistent production of safe and assured quality blood components in blood establishments, including related donor safety concerns. The document is intended to serve as guidance for both blood establishments and NRAs when implementing and enforcing these principles. It does not address the practice of transfusion medicine or management of emergencies or crises where specific policies defined by the NRA apply. Aspects of personnel and environmental protection are also not within the scope of this document.

Complementary guidance, especially with respect to the production of plasma for fractionation, is available in the *WHO recommendations for the production, control and regulation of human plasma for fractionation* (3).

2. Glossary and abbreviations

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

apheresis

The process by which one or more blood components are selectively obtained from a donor by withdrawing whole blood, separating it by centrifugation and/or filtration into its components, and returning those not required to the donor.

blood collection

The procedure whereby a single donation of blood is collected in an anticoagulant and/or stabilizing solution, under conditions designed to minimize microbial contamination, cellular damage and/or coagulation activation of the resulting blood donation.

blood component

A constituent of blood (erythrocytes, leukocytes, platelets, cryoprecipitate and plasma) that can be prepared by various separation methods and under such conditions that it can be used either directly for therapeutic purposes or for further processing/manufacturing.

blood establishment

Any structure, facility or body that is responsible for any aspect of the collection, testing, processing, storage, release and/or distribution of human blood or blood components when intended for transfusion or further industrial manufacturing.

blood products

Any therapeutic substances derived from human blood, including whole blood, blood components and plasma-derived medicinal products.

calibration

The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

CJD/vCJD

Creutzfeld-Jakob-Disease/variant Creutzfeld-Jakob-Disease.

closed system

A system developed for aseptic collection and separation of blood and blood components, manufactured under clean conditions, sealed to the external environment and sterilized by a validated and approved method.

computerized system

A system including the input of data, electronic processing and the output of information to be used either for reporting or for automatic control.

contract acceptor

An establishment or institution that performs particular work or services under a contract for a different institution.

contract giver

An establishment or institution that is subcontracting particular work or services to a different institution and sets up a contract defining the duties and responsibilities of each side.

donor

A person in defined good health conditions who voluntarily donates blood or blood components, including plasma for fractionation.

distribution

The act of delivery of blood and blood components to other blood establishments, hospital blood banks or manufacturers of blood- and plasma-derived medicinal products. It does not include the issuing of blood or blood components for transfusion.

first-time (tested) donor

A donor whose blood or plasma is tested for the first time for infectious disease markers in a blood establishment.

good manufacturing practice (GMP)

All elements in the established practice that will collectively lead to final products or services that consistently meet appropriate specifications and compliance with defined regulations.

HAV, hepatitis A virus

A non-enveloped single-stranded RNA virus that is the causative agent of hepatitis A.

HBsAg, hepatitis B surface antigen

The antigen on the periphery of the hepatitis B virus.

HBV, hepatitis B virus

An enveloped double-stranded DNA virus that is the causative agent of hepatitis B.

HCV, hepatitis C virus

An enveloped single-stranded, RNA virus that is the causative agent of hepatitis C.

HIV, human immunodeficiency virus

An enveloped, single-stranded RNA virus that is the causative agent of the acquired immunodeficiency syndrome (AIDS).

HTLV 1 and 2, human T-cell lymphotropic virus, types 1 and 2

Enveloped, single stranded RNA viruses that are typically cell-associated.

manufacture

All operational processes or steps — including purchase or selection of materials and products, production, quality control, release, storage and distribution of products and the related controls — used to produce a blood product. This includes also the donation process.

mobile site

A unit or site used for the collection of blood and/or blood components, operating temporarily or at movable locations off-site from a permanent collection site, under the responsibility of a blood establishment.

nucleic acid amplification techniques (NAT)

A testing method to detect the presence of a targeted area of a defined microbial genome that uses amplification techniques such as polymerase chain reaction (PCR).

near-miss event

An incident that, if not detected in a timely manner, would have affected the safety of the recipients or donors.

national regulatory authority (NRA)

WHO terminology for national medicines regulatory authorities. NRAs should promulgate and enforce medicines regulations.

plasma for fractionation

The liquid part of human blood remaining after separation of the cellular elements from blood collected in a container containing an anticoagulant, or separated by continuous filtration and/or centrifugation of anticoagulated blood in an apheresis procedure, intended for further manufacturing.

production

All operations involved in the preparation of blood components, from collection through processing to completion as a finished product (blood component).

qualification

A set of actions used to provide documented evidence that any piece of equipment, critical material or reagent used to produce the final product and that might affect the quality or safety of a product works reliably as intended or specified and leads to the expected results.

quality

The total set of characteristics of an entity that affect its ability to satisfy stated and implied needs, and the consistent and reliable performance of services or products in conformity with specified requirements. Implied needs include safety and quality attributes of products intended both for therapeutic use and as starting materials for further manufacturing.

quality assurance

A part of quality management focused on providing confidence that quality requirements will be met.

quality management

The coordinated activities that direct and control an organization with regard to quality.

quality management system

A management system that directs and controls an organization with respect to quality and that ensures that steps, processes, procedures and policies related to quality activities are being followed.

quality risk management (QRM)

A systematic process for the assessment, control, communication and review of risks to the quality of the product across the product's life cycle.

quarantine

The status of starting or packaging materials, intermediate, bulk or finished products that are isolated physically or by other means while a decision is awaited on their release for use or rejection.

regular donor

A person who routinely donates blood, blood components or plasma in the same blood establishment in accordance with the minimum time intervals.

repeat donor

A person who has donated before in the same establishment but not within the period of time considered as regular donation.

repeatedly reactive

A donation is considered to be repeatedly reactive if it is found reactive in a screening test, is retested in duplicate using the same assay, and at least one of the repeat tests is also reactive.

validation

Actions for proving that any operational procedure, process, activity or system leads to the expected results. Validation work is normally performed in advance according to a defined and approved protocol that describes tests and acceptance criteria.

WNV, West Nile Virus

An enveloped single-stranded RNA virus that is the causative agent of West Nile fever.

3. Quality management

3.1 Principles

Quality is the responsibility of all persons involved in the various processes of the blood establishment. The management of the blood establishment is responsible for a systematic approach to quality and the implementation and maintenance of a quality management system. A quality programme should be designed to ensure that each product (including plasma for fractionation) is manufactured in the same manner from donor selection through to distribution of the final product.

Quality management involves all activities that determine the quality policy, objectives and responsibilities, and their implementation through quality planning,

quality control, quality assurance and quality improvement in order to assure the quality and safety of blood and blood components.

The attainment of the quality policy and objectives is the responsibility of the senior management of the blood establishment and requires the participation and commitment of all staff throughout the entire blood establishment. Senior management should review the quality system at regular intervals to verify its effectiveness and to introduce corrective measures if they are considered necessary.

Within the organizational structure of the blood establishment there should be a quality management unit comprising one or more persons. The quality management personnel should be responsible for ensuring that there is documented evidence that the quality policies, procedures and practices are being fulfilled. Senior management, in coordination with the quality management unit, should develop and implement quality assurance policies and objectives in a manner that provides clear direction to all staff. The quality assurance policies and objectives should be designed to ensure the highest levels of safety and quality in the blood components that are produced from each collection. The policies and procedures should comply with all national and, where appropriate, international regulations and requirements.

Staff should be able to understand the intent of the quality objectives and their own role in accomplishing the objectives. The performance of the quality management system should be evaluated periodically by determining whether the objectives have been or are continuously being met. If there are shortcomings in the quality system, corrections should be made and the quality management unit should be held responsible for monitoring corrective action and continued compliance.

Within any blood establishment there should be independent functions for fulfilling quality assurance and quality control responsibilities. The quality assurance function should be independent of manufacturing operations and should assure that all processes are performed and documented. The quality assurance function should be involved in all quality-related matters and in the review and approval of all quality-related documents.

3.2 Quality assurance

Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of the product. It is the totality of arrangements that are made with the purpose of ensuring that products are of the quality required for their intended use. Quality assurance therefore incorporates GMP, and other elements, including those outside the scope of this guideline — such as product design and development (7).

Quality assurance is that part of quality management that ensures that all critical processes are appropriately described in written instructions (see chapter 5), are performed in accordance with the principles of GMP and comply with the appropriate regulations. The quality assurance system should be fully documented, distributed and explained to everyone involved in the manufacturing processes.

All parts of the quality assurance system should be adequately resourced with competent personnel, suitable premises, and suitable and sufficient equipment and facilities to enable the manufacturing steps to be completed in a safe and quality-compliant manner.

3.2.1 Good manufacturing practice in blood establishments

GMP is the part of quality assurance that ensures that blood products are consistently produced and controlled to the quality standards appropriate to their intended use, as required by predefined specifications and, if applicable, by the marketing authorization. GMP is aimed primarily at diminishing the risks inherent in any blood establishment operation — such as contamination (including cross-contamination), mix-ups, disease transmission or other unexpected adverse outcomes resulting from the use of blood products. GMP is concerned with both production and quality control.

The basic requirements of GMP are the following:

- All manufacturing processes are clearly defined by policies and standard operating procedures, are systematically reviewed in the light of experience, and are shown to be capable of consistently manufacturing products of the required quality that comply with their specifications.
- Qualification of equipment and reagents and validation of processes and methods are performed prior to use in the manufacture of products intended for transfusion or further manufacturing.
- All necessary resources are provided — including appropriately qualified and trained personnel, adequate premises, suitable equipment, appropriate materials, approved procedures and instructions, suitable storage and transport.
- A system is available to maintain traceability of all released products in order to facilitate recall, if necessary, of any product suspected of not conforming to standards, and there is also a system to handle complaints.
- A system is available that addresses process and quality improvement functions and activities.

3.2.2 Quality control

Quality control is that part of GMP which is concerned with specifications, sampling and testing. Quality control is also concerned with the organization, documentation and release procedures which ensure that the necessary and relevant tests are carried out and that neither materials are released for use nor products released for supply until their quality has been judged to be satisfactory (7). For quality control programmes in blood establishments, refer to sections 9.5 and 9.6.

3.3 Product quality review

Regular periodic or rolling quality reviews should be conducted with the objective of verifying the consistency of the existing process and the appropriateness of current specifications in order to highlight trends and to identify improvements in both product and process.

A product quality review may also be considered as an instrument for surveying the overall quality status of a blood component and its manufacturing processes, including the collection of starting materials. Such a review should normally be conducted annually and should be documented. In accordance with international and/or NRA requirements and recommendations it may include:

- review of starting materials;
- review of critical in-process controls;
- review of results of quality control and quality monitoring;
- review of all changes;
- review of the qualification status of equipment;
- review of technical agreements and contracts;
- review of all significant deviations, errors and non-conformances, and the corrective actions implemented;
- review of the findings of internal audits and other inspections, and the corrective actions implemented;
- review of complaints and recalls;
- review of donor acceptance criteria;
- review of donor deferrals;
- review of look-back cases.

3.4 Quality risk management

Blood establishments should ensure that blood components manufactured in their facilities are of the quality required for their intended use, comply with quality standard requirements, and do not place recipients at risk due to inadequate safety, quality or efficacy throughout the life-cycle of the product. In order to reliably achieve the quality objective, there should be a comprehensively designed and correctly implemented system of quality assurance that incorporates GMP, quality control and quality risk management (QRM).

An effective QRM approach can ensure the quality of a product by providing proactive means to identify and control potential quality issues. It can also facilitate and improve the decision-making process in cases when quality problems or deviations from standard processes and specifications have to be assessed or planned changes need to be evaluated.

The two primary principles of QRM are:

- The evaluation of the risk to quality and safety should be based on scientific knowledge and ultimately linked to the protection of the donor and/or recipient.
- The level of effort, formality and documentation of the QRM process should be commensurate with the level of risk.

Examples of the QRM processes and applications can be found in guidelines on QRM, such as the Q9 guideline of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (8). This describes processes and offers a selection of methods and tools for applying the QRM principles.

3.5 Change control

A formal change control system should be in place to plan, evaluate and document all changes that may affect the quality, traceability and availability of blood or blood components or that might have an impact on the safety of blood, blood components, donors or recipients. The change control system should guarantee a formal approval of a change before it is implemented. Furthermore it should ensure that the impact of the proposed change is assessed and that all necessary measures — such as qualification and validation, training of personnel, adoption of working instructions, revision of contracts, definition of maintenance tasks, information for third parties and authorities — are defined and completed at the time the change is put into force. The need for additional testing and validation should be determined on a scientific basis. A risk analysis may be appropriate as part of the QRM.

After the implementation of a change, a post-implementation evaluation should be carried out in order to determine whether the introduction of the change has been successful and effective.

The introduction of new equipment, processes and methods should be treated as a change.

3.6 Deviation evaluation and reporting

Any deviation from standard operating procedures, validated processes, or non-conformances with specifications or other quality-related requirements should be recorded and investigated. The potential impact on the quality of the product in question, or on other products, should be evaluated.

The evaluation of the cause of the deviation and of related processes that may also be implicated in the deviation should be documented. Review and approval of the investigation as completed should be documented by the quality assurance and/or quality control department as appropriate.

All deviations and non-conformances should be logged in a system that allows for appropriate data review. A data review should be carried out periodically in a manner that allows for tracking and trending of data and that facilitates process improvement.

The handling of deviations and non-conformances should be defined in writing. Actions should be taken within a reasonable time frame in order to avoid any impact on other products manufactured within the same establishment.

Under certain circumstances a product may be accepted after evaluation of a deviation. The documentation should include the justification or rationale for accepting a product manufactured in deviation from a specified requirement, and should be signed by the responsible person.

3.7 Corrective and preventive actions

A corrective and preventive action system should be established, implemented and maintained to ensure that there is continuous improvement at the blood establishment. The procedures should include the management of deviations and non-conformances, complaints, events and findings of the quality system management review, inspections and audits, and should ensure the proper recording of all corrective and preventive actions taken.

The corrective and preventive action system should ensure that each quality problem is addressed and corrected and that recurrence of the problem is prevented. Actions should be carried out within a reasonable predefined time frame. The management of the blood establishment should be involved in the review of corrective and preventive actions.

The blood establishment should have methods and procedures in place to collect, document and evaluate data on quality. Product or quality problems should be entered into the corrective and preventive action system. Quality data include all errors, deviations, non-conformances, accidents, near-miss events and complaints. Quality data also include the results of quality control tests and monitoring activities. Quality data should be reviewed at defined intervals in order to identify product and quality problems that may require corrective action and to identify unfavourable trends that may require preventive action.

3.8 Internal audits

In order to monitor implementation and compliance with the quality management system, regular internal audits should be performed according to an established procedure. Internal audits should be conducted by trained, independent and competent persons under the responsibility of the organization's quality assurance unit.

Internal audits should be arranged according to a schedule and should cover all parts of the operations, including data processing systems. Each audit should be carried out according to an approved audit plan that assesses compliance with internal

requirements and applicable national and/or international regulations.

All audit results should be documented and reported to the management. Appropriate corrective and preventive actions should be taken in a timely and effective manner and should be assessed for effectiveness after implementation.

The quality assurance department, where the internal audit function resides, should not audit itself but should be subject to an independent audit.

Internal audits are not a substitute for official inspections performed by the competent national authorities who check compliance with national regulations.

3.9 Complaints and product recall

3.9.1 Complaints

There should be a system in place to ensure that all complaints are handled according to written — and approved — standard operating procedures. The review of the complaint should take account of whether the complaint relates to a quality defect in a blood component. The blood establishment should determine whether a recall should be initiated. The process should be defined in a standard operating procedure. Complaints, adverse events or reactions, as well as any information concerning potentially defective products, should be carefully reviewed and thoroughly investigated in order to find the root cause of the problem. Consideration should be given to determining whether other products are also affected. All investigations and actions should be carried out in a timely manner to ensure that the safety of the recipient is not compromised and that other products manufactured within the same establishment are not affected.

Immediate corrective actions should be taken to address the root cause of the problem, and actions should be taken to prevent it from recurring. There should be active follow-up of the implementation of corrective actions (see section 3.7).

Designated personnel should be responsible for managing complaints and coordinating investigations, actions and measures to be taken within a defined time frame. The unit responsible for quality should be included in this process.

All complaints, with the original details, should be recorded. Records should be retained of all the decisions, investigations and measures taken as a result of a complaint. Complaint records should be reviewed regularly in order to check for unfavourable trends or recurring problems and to ensure continuous quality improvement.

Depending on the national requirements the NRA should be informed.

3.9.2 Recalls

An effective written recall procedure should be in place, including a description of the responsibilities and actions to be taken. A recall should always be initiated whenever it is discovered that a product does not meet the release criteria of the blood establishment and NRA. This may happen when information is obtained subsequent to the release of a product and, had this information been known in advance, it would have prevented

the blood component from being released. A recall may also be indicated when it is discovered that personnel did not follow standard operating procedures. Corrective actions should take place within predefined time periods and should include the traceability of all relevant components and, where applicable, look-back procedures (see section 3.11).

A qualified person within the blood establishment should be nominated to assess the need for product recall and to initiate, coordinate and document the necessary actions.

Recall operations should be initiated promptly and at any time. Therefore the standard operating procedures should include emergency and “out of hours” contact details. Depending on the national requirements the NRA should be informed.

Recalled products should be destroyed. If recalled products are not destroyed, they should be clearly identified and stored separately in a secure area.

3.10 Process improvement

Ideas for potential improvements to any of the systems may come from research, development, brainstorming, or from the management of non-conformances, events and complaints, from internal or external audit or inspection findings, and from deviations detected during quality monitoring activities.

The process should track corrective or preventive actions that are developed and implemented. An effectiveness check should be in place to determine the impact or effectiveness of any changes. These activities should be documented and reported at least annually to the executive management (in the quality management review report).

3.11 Look-back

A written system should be in place for carrying out a look-back procedure. This process should be able to trace the products collected from a donor to the final recipients and from the recipient back to the donor, preferably by means of a computer database.

This standard operating procedure should be followed when it is determined retrospectively that a blood or plasma donation should have been excluded from processing — for instance, because the unit was collected from a donor who was subsequently rejected for reactive viral marker, high-risk behaviour, exposure to CJD/vCJD or other risks related to infectious diseases (*donor look-back*) (3).

If a donor is confirmed to have a disease that is transmissible by blood products or has high-risk behaviour, the donor should be permanently excluded from further donation. All donations from such a donor should be traced and prevented from being used or further manufactured unless they have expired and therefore have already been destroyed. If donations have been used or further processed, procedures should be in place to define appropriate actions. Donor notification and counselling is recommended for purposes of donor health and for the safety of the blood supply.

There should be a process in place for investigating a report of a suspected transfusion-associated reaction in a recipient, in order to identify a potentially implicated donor (*recipient look-back*). The donor of products implicated in transmitting disease or causing recipient harm should be excluded from further donations. All other donations from the implicated donor should be traced and blood components removed from the inventory and recalled, if within the expiry date.

All post-donation information should be recorded and maintained. There should be a system in place to react accordingly and in time to remove unexpired products from distribution in order to assure the safety of recipients.

The recipients of any products identified in the look-back process should be counselled about the risk of having contracted a disease from the potentially contaminated products and should be offered disease marker testing, consultation and medical treatment if indicated. For plasma used for fractionation, the manufacturer of the medicinal product should be notified in case of a look-back (3).

4. Personnel

Sufficient personnel should be available and should be qualified to perform their tasks. They should have the appropriate qualifications and experience and should be given initial and continuous training in order to assure the quality and safety of blood and blood components.

Only persons who are competent in the manufacturing process and have read and understood all relevant standard operating procedures should be involved in the manufacturing and distribution processes, including collection, quality control and quality assurance.

4.1 Organization and responsibilities

Tasks and responsibilities should be clearly documented and understood. Personnel should have clear, current and written job descriptions. There should be an organizational chart showing the hierarchical structure of the blood establishment with clear delineation of lines of responsibility and reporting.

Key personnel include the following functions and their substitutes:

- a “responsible person” (see functions and qualifications below);
- a processing or operations manager, responsible for all processing and operations activities;
- a quality control manager, responsible for all quality control activities;
- a quality assurance manager, reporting findings or quality issues directly to the responsible person and empowered to discontinue operations if quality and safety expectations are not being fulfilled;

- a physician with the responsibility to ensure the safety of donors and the safety of the distributed blood components.

The blood establishment should nominate a “responsible person” who will be responsible for:

- ensuring that approved donor selection criteria are followed;
- ensuring that every unit of blood or blood components has been collected, tested, processed, stored and distributed in compliance with the national regulations in force;
- providing information to the competent national authority;
- ensuring that the required initial and ongoing training of personnel is carried out;
- ensuring that a quality management system and a haemovigilance system (ensuring traceability as well as notification of serious adverse events and reactions) is in place in the blood establishment.

The responsible person should fulfil the qualification requirements according to the national regulations, or should fulfil the following minimum conditions of qualification:

- He/she should hold a diploma, certificate or other evidence of formal qualification in the field of medical or biological sciences awarded on completion of a university course of study or a course recognized as equivalent.
- He/she should have practical experience in relevant areas, preferably for at least two years, in one or more establishments which are authorized to undertake activities related to collection, testing, preparation, storage and distribution of blood and blood components.

Depending on the national legislation, the name of the responsible person may need to be communicated to the NRA.

The quality assurance manager and the processing or operations manager should be different persons, functioning independently. The quality assurance manager is responsible for ensuring that there are appropriate quality systems and protocols in place for the safe and secure release of all materials, equipment, reagents and blood and blood components.

The processing or operations manager is responsible for ensuring that there are appropriate manufacturing and technical processes and procedures in place for the production of blood or blood components.

The physician should hold a relevant medical degree awarded on completion of a university course of study and should hold any registration or licensure that is required by the national authority.

Responsibilities should be delegated only to individuals who have been trained for the task. Delegation should be in written form and should be reviewed regularly.

4.2 Training

Personnel should receive initial and continuous training that is appropriate to their specific tasks. This training should be carried out by qualified personnel or trainers and should follow prearranged written programmes. Approved training programmes should be in place and should also include:

- relevant principles of transfusion medicine;
- GMP;
- relevant knowledge in microbiology and hygiene.

Training should be documented and training records should be retained.

4.2.1 Initial training

Programmes for the initial training of newly recruited personnel or personnel taking over new functions should take into account all relevant tasks and procedures, including general topics such as quality assurance, GMP and computerized systems. The same topics and principles apply to training aimed to reintroduce personnel after a longer absence from the workplace. The time frames should be defined.

The training records should identify at least the trainer, all the specified tasks (including the relevant standard operating procedures) and when the training was completed. The records should be signed by both the trainee and the trainer. Upon completing the training, the personnel should be competent in the tasks in which they have been trained. If a database is used the personnel training profile should be updated annually.

4.2.2 Continuous training

Continuous training programmes (theoretical and/or practical training) should be in place to ensure that personnel keep up the skills to carry out their assigned tasks. Such training programmes should take technical and scientific developments into account. Training should also include any changes to standard operating procedures and personnel requirements. Both internal and external training courses may be useful here.

4.2.3 Competency

The overall competency of personnel is a result of education, experience and training. As a key factor for the quality and safety of blood and blood products, competency has to be carefully evaluated and continuously monitored.

Upon completion of the initial training, the competency of the personnel should be evaluated and documented. After the initial competency is determined, there should be periodic assessment of competency. The contents of training programmes and their effectiveness should be periodically reviewed and assessed.

4.3 Personal hygiene

All personnel, prior to being hired and during employment, as appropriate, should undergo health examinations. Any person shown at any time to have an illness or open lesions that may adversely affect the quality of the products and/or the safety of the donors should be excluded from the establishment's manufacturing processes until that person's condition is no longer judged to be a risk.

All personnel should be trained in personal hygiene. In particular, personnel should be instructed to wash and disinfect their hands before, during and after activities such as blood collection and production.

Special attention should be drawn to the need to protect donors, employees and products from contamination — especially with blood and any other material of human origin.

To ensure protection of products, donors and employees from contamination, personnel should wear clean protective clothing appropriate for the duties they perform. Soiled protective clothing, if reusable, should be stored in a separate closed container until properly laundered and, if necessary, disinfected or sterilized. Where appropriate, disposable or sterile gloves should be worn when handling items that may come in contact with any blood or blood components.

Smoking, eating, drinking, chewing, and keeping plants, food, drinks, smoking material and personal medicines should not be permitted in areas used for production, testing, storage or distribution, or in other areas where they might adversely affect product quality. Personal hygiene procedures, including the use of appropriate protective clothing and equipment, should apply to all persons entering production areas.

5. Documentation

The documentation of procedures and records is essential to the quality assurance system. It ensures that work is performed in a standardized and uniform manner and ensures the traceability of all steps. Written instructions should include all applicable methods and procedures and should be accessible to all authorized personnel.

5.1 Standard operating procedures and records

5.1.1 Standard operating procedures

All critical procedures — such as purchase and receipt of starting materials, selection of donors, collection of blood, preparation of blood components, laboratory testing and

associated quality control testing, product labelling, storage, release, dispatch, shipping, and recall of final products — should be specified in appropriate written instructions in accordance with the principles of GMP and relevant national regulations. Quality assurance procedures such as complaint investigations, deviation management, recall of non-conforming products, change control and document control should also be specified in written instructions.

All activities should be carried out according to the standard operating procedures. The standard operating procedures and the processes should be regularly reviewed and updated as necessary in order to improve the quality of products and services delivered. The document review process should itself be documented.

5.1.2 Records

Each activity that may affect the quality of blood and blood components should be documented and recorded at the time it takes place. Critical activities should be double-checked, either by a second person or electronically. There should be documentation to ensure that work is performed in a standardized manner according to standard operating procedures and that all critical steps in the process are traceable — especially those that have the potential to affect the quality of the product. The documentation should allow all steps and all data to be confirmed by independent review. All documentation should indicate the person performing the action, the date of the action and the equipment used in the action, where applicable.

Records should be legible, accurate, reliable and a true representation of the results and entries. The legibility of records is of great importance. Handwritten entry of data should be clear. Corrections to any records should be made in a manner that permits the reading and review of the previous entry, the correction, the date of correction and the person responsible for the correction.

Critical manufacturing and laboratory testing records should be reviewed frequently for completeness, legibility and, when appropriate, accuracy by the manager or other designated person.

5.2 Document control

All documents should be laid out in an orderly manner with a unique title and reference number, and should indicate the version and the effective date. The content of the document should be clear and should not include superfluous information. Title, nature, purpose and scope should be clearly outlined. Documents should be reviewed, approved, signed and dated by authorized persons. An audit trail should indicate the person responsible for each step of document control.

5.2.1 Document management

A document management system should be in place. Documents that outline specific manufacturing steps or other critical steps should be readily available to the personnel

performing these tasks. A document control standard operating procedure should be established for the development, review, approval, distribution, implementation, revision and archival of documents. When a document has been revised, the document management system should function in such a way as to prevent the inadvertent use of documents that have been superseded.

There should be a record of the distribution of each document which also shows at least the work areas or tasks affected by the document. All changes to documents should be acted upon promptly and should be reviewed, dated and signed by a person authorized to do so. Standard operating procedures should be designed, developed and approved, and personnel trained in a consistent manner, prior to implementation.

5.2.2 Record retention and archiving

All records, including raw data, which are critical to the safety and quality of blood or blood components, should be kept in a secured storage area according to national regulations, or preferably for at least 10 years. A longer period for retention of records may be required by NRAs, international requirements or by specific contractual agreements. Records of permanently deferred donors should be kept indefinitely.

Outdated standard operating procedures should also be kept in a historic file system. Documents should be archived in a secured area and should be readily accessible for retrieval by authorized personnel if required. The archival and retrieval process, especially if computerized systems are used, should be validated to ensure that all information can be retrieved and read at any time until the end of the required period of retention.

6. Premises and equipment

6.1 Premises

6.1.1 Design and construction

Premises should be located, constructed, adapted and maintained to suit the operations that are to be carried out in them. Premises should be designed to permit effective cleaning and maintenance to minimize risk of contamination. The workflow should be designed and arranged to allow for a logical flow of staff, donors and products in order to minimize the risk of errors. Working areas should not be used as passageways or storage areas.

Ancillary areas should be separated from the donor evaluation area, and from the screening, collection and manufacturing areas. Washing and toilet facilities and, if required, facilities for changing or eating should be maintained in a hygienic and tidy condition.

Production, testing and storage areas should be secured against entry by unauthorized persons.

Lighting, temperature, humidity and ventilation should be appropriate and should not adversely affect production or storage. Premises should be designed and equipped so as to afford maximum protection against the entry of animals, including insects.

Premises should be carefully maintained and cleaned (see sections 6.2.2 and 6.2.3) and where appropriate disinfected according to detailed written standard operating procedures. Cleaning records should be retained.

6.1.2 Donor areas

The area for blood donors should be separated from all production and testing areas.

The design of premises should be adequate for the conduct of operations and should allow for the logical flow of donors, in one direction if possible, so that donors who have passed reception, screening and donation do not have to return to a previous area.

The area for donor selection should permit confidential personal interviews to take place with due consideration for the safety of donors and personnel.

Rest and refreshment rooms for donors should be separated from donation or storage areas.

6.1.3 Production areas

Blood processing should be carried out in adequate facilities that are suitable for the purpose. The donor area, and production and testing areas should be separated from each other.

Whenever possible, closed systems should be used. Using a validated sterile connecting device creates a functionally closed system.

When the use of a closed system is not possible or not appropriate, the risk of contamination or cross-contamination needs to be minimized. Therefore, the premises used for the processing of blood components in an open process should be designed and qualified as a grade A environment with a grade B background, as defined in the WHO GMP for sterile pharmaceutical products (12). A less stringent environment may be acceptable if the preparation of the product is directly combined with additional safety measures — such as immediate transfusion within a defined and limited time period after processing, or placing the product immediately into storage conditions that prohibit microbial growth. Personnel performing open processing should wear appropriate clothing (i.e. suitable coats, masks or gloves) and should receive regular training in aseptic manipulations. Aseptic processing should be validated. Environmental monitoring protocols should be applied and evaluated by the quality assurance unit.

The premises used for processing blood components should be kept in a clean and hygienic condition. Monitoring of the microbiological contamination load should be considered for critical equipment surfaces and environments where appropriate, according to a risk-based assessment of the process. Records should be available.

Each area of processing and storage should be secured against entry by unauthorized persons and should be used only for the intended purpose.

6.1.4 Storage areas

Storage areas should provide adequate space and should be arranged in a way that allows for dry and orderly placement of stored materials.

Storage conditions should be controlled, monitored and documented to show compliance with the specifications. Equal distribution of temperature throughout the storage facility should be guaranteed and documented. This is particularly important for the critical materials used in processing blood and blood components. Temperature checks should be carried out and recorded at least daily. Appropriate alarms at upper and lower temperature limits should be present and should be regularly checked; the checks should be recorded. Appropriate actions to be taken when there is an alarm should be defined in writing.

Intermediate storage and transport should be carried out under defined conditions to ensure that specifications are met.

Storage areas should provide effective segregation of quarantined and released materials or components. There should be a separate area for rejected components and materials.

6.1.5 Laboratories

Testing laboratories should be designed and constructed so as to minimize the risk of errors and contamination. Laboratory areas should be separated from the processing and final product storage areas. Where nucleic acid amplification testing (NAT) technology warrants, separate premises (rooms) and air handling systems should be considered for performing NAT. Consideration should be given to constructing a separate room for specimen sampling and another room for amplification and nucleic acid detection in order to minimize the risk of contamination or false-positive test results.

6.1.6 Mobile collection sites

Premises for mobile collection sites should be adequate in design for the conduct of operations and should allow for the logical flow of staff, donors and products in order to minimize the risk of errors. The blood collection at mobile sites should be planned thoroughly. Ancillary areas (rest and refreshment rooms) should be separated from donation or storage areas, but observation of donors during post-donation refreshment should still be ensured.

Before premises are accepted for mobile donor sessions their suitability should be assessed against the following criteria:

- sufficient size to allow proper operation and ensure donor privacy;
- safety for staff and donors;

- ventilation, electrical supply, lighting, hand-washing facilities, reliable communication, sufficient space for blood storage and transport, and suitable temperature conditions.

Each site should have an approved plan that details the site layout. The set-up of the mobile collection site should be carried out according to the approved plan.

6.2 Equipment

6.2.1 Design and construction

All equipment should be designed and installed to suit its intended purpose and should not present any hazard to donors, personnel or blood components. It should allow for effective cleaning, and disinfection is recommended for all surfaces in direct contact with the bag system.

Equipment should be located in a suitable position (e.g. a balance should be positioned on a suitable even surface) where there is no negative impact from the surrounding environment (e.g. direct sunlight may have an impact on optical instruments such as apheresis systems or balances).

6.2.2 Maintenance

Maintenance, cleaning and calibration should be performed regularly and should be recorded. Maintenance of equipment should be carried out at intervals according to a documented schedule.

The maintenance programmes should be established on the basis of qualification activities. The intervals should be defined according to the instructions of the manufacturer of the equipment. Where intervals are not defined by the equipment manufacturer, maintenance should be carried out at least annually. Different intervals may be defined on the basis of a risk assessment. If no regular maintenance activities are recommended by the manufacturer, at least a functional control should be performed according to documented procedures. All maintenance activities should be documented. The maintenance reports of external technical services should be checked and countersigned by the staff of the blood establishment in order to decide if action needs to be taken as a result of the maintenance outcome. The maintenance documents should include sufficient information to determine what types of checks have been performed.

Maintenance should also be carried out on equipment that is not in regular use, including back-up systems.

Instructions for use, maintenance, service, cleaning and sanitization should be available in a language that is understood by the user. There should be written procedures for each type of equipment, detailing the actions to be taken when malfunctions or failures occur. Defective equipment, or equipment that is not in service, should be clearly labelled and if possible removed from the working area.

The maintenance of sterile connecting devices should include a check of the tensile strength. Furthermore, as it is a very critical piece of equipment, there should be regular functional checks of the integrity of the tubing weld.

In general, functional tests should also be considered for other pieces of equipment — such as for balances before use after they have been moved or transported to a mobile site.

A regular maintenance programme, including appropriate intervals, should be in place for all critical laboratory equipment or systems. A procedure should be implemented for releasing equipment after maintenance or intervention.

If the maintenance is contracted out (e.g. to the supplier) the work should be documented. Equipment should be evaluated to determine if it is still capable of expected performance prior to returning it to service for manufacturing blood components.

6.2.3 Cleaning

Cleaning procedures should be established and described in a standard operating procedure. Cleaning of equipment should take into consideration the instructions of the manufacturer. A schedule for regular cleaning and disinfection, if necessary, is recommended for all surfaces with direct contact with the bag system (e.g. centrifuge, separator, storage shelves).

Disinfectant solutions with sufficient and approved antimicrobial activity should be used. A cleaning plan should be established that specifies the cleaning intervals and methods to be used for the different equipment and premises. The cleaning procedures should not impact negatively on the equipment or blood components. Cleaning activities should be documented.

6.2.4 Calibration

Measuring instruments and measuring systems used for the collection and further separation of blood and for quality control testing should be calibrated regularly according to the instructions of the manufacturer. Calibration should be carried out and documented according to established standard operating procedures and national regulations. Regular calibration is necessary for temperature probes (e.g. in refrigerators), pipettes, balances, timing devices and haemoglobinometer devices (using control blood and/or cuvettes from the manufacturer). The devices used for calibration, such as the control weight used for the calibration of balances, should be certified for accuracy (by testing against a known standard). If the calibration consists of using a comparison measurement approach with a second device, then the maximum allowed deviation between the two measurements should be defined.

6.3 Computerized systems

A computerized system may be described as a functional unit consisting of one or more computers and associated peripheral input and output devices, and associated

software that uses common storage for all or part of a programme and for all parts of the data necessary for the execution of the programme (9). A computerized system executes user-written or user-designated programmes, performs user-designated data manipulation (including arithmetic operations and logic operations), and it can execute programmes that modify themselves during their execution. A computer system may be a stand-alone unit or may consist of several interconnected units.

Hardware and software should be protected against unauthorized use or changes.

Critical computerized systems should be validated before use. The system is considered critical if:

- it is directly linked to the decision-making process for blood product manufacturing, blood or blood product testing (donor/recipient), labelling and release;
- it is used to handle or manipulate the related information;
- it has an impact on product quality, information management, storage, or tools for operational decision-making and control.

Periodic revalidation or annual checks to ensure reliability should be performed on the basis of a risk assessment.

There should be procedures for each type of software and hardware, detailing the action to be taken when malfunctions or failures occur. A back-up procedure should be in place to prevent loss of records in case of expected or unexpected downtime or function failures. The archival and retrieval process should be validated to ensure the accuracy of the stored and retrieved data.

Once in routine operation, critical computer systems should be maintained in a validated state. Any change should be handled through the formal change control system which includes qualification and/or validation activities. Applicable documentation should be revised and personnel should be trained before the change is introduced into routine use. Any software updates should be evaluated in advance and there should be procedures to validate or verify the acceptability of the update installation.

The manual entry of critical data, such as laboratory test results, should require independent verification and release by a second person. When a computerized system is used, an audit trail should be guaranteed.

7. Qualification and validation

7.1 Qualification of equipment

All equipment should be qualified and used in accordance with validated procedures.

New and repaired equipment should meet qualification requirements when installed and should be authorized before use. Qualification results should be documented.

The extent of qualification depends on the critical nature and complexity of the equipment. For some equipment, installation qualification and calibration may be sufficient. More complex equipment may need a more thorough approach to qualification and validation and should include the instruments, the associated operation(s) and the software involved.

Further guidance on qualification and validation is given in the WHO guidelines on validation (10) and in the Pharmaceutical Inspection Co-operation Scheme (PIC/S) *Recommendations on validation master plan, installation and operational qualification, non-sterile process validation, cleaning validation* (11).

7.2 Validation of manufacturing processes

All critical processes in the manufacture of blood and blood components should be validated before implementation according to a predefined protocol of tests and acceptance criteria. Critical processes include donor selection and determination of suitability, component preparations, donor testing for infectious diseases (see also section 7.3), ABO blood typing and antibody screening where applicable (e.g. for red-cell concentrates), labelling, storage and distribution.

Validation studies, including statistically based sampling where feasible, should be conducted to ensure that products are produced with consistent quality characteristics. Acceptance criteria should be based on a defined set of specifications for each blood component, including a set of quality control tests — such as measurement of weight respective to volume, residual blood cells (depending on product specifications), haemoglobin, and relevant coagulation factors (e.g. Factor VIII) and/or total protein/IgG content where applicable — established by the blood establishment or the NRA (see also sections 9.4.3 and 9.6). Data should be available to ensure that the final product is able to meet specifications.

Likewise, apheresis systems, including software, should be qualified and maintained. Apheresis procedures should be validated. Validation criteria with regard to the quality of blood components may, depending on the product, include weight, yield, content of residual white blood cells, haemoglobin and relevant coagulation factors. Validation studies of new apheresis procedures should also evaluate possible risks of activation of the coagulation, fibrinolysis, and complement systems potentially induced by the material in contact with blood. Such studies are usually performed by the manufacturer of the apheresis systems to support the licensing by the regulatory authorities.

7.3 Choosing an appropriate test system to screen for infectious disease

The quality of the screening of blood donations for markers of infection depends on a number of conditions being fulfilled:

- Only test systems designed and validated for blood donor screening should be used. Other systems, such as tests validated for diagnostic purposes only, should not be used.
- All test systems should be validated by the manufacturer.
- Before implementing a test system for routine analysis, the laboratory should prove by validation that the manufacturer's specifications are met (in principle this also applies if in-house tests are used).
- The laboratory should show that, on routine application of test systems, specified performance is reached and is consistently maintained.

Screening of blood donations generally requires such test systems to aim for high sensitivity even though this may be achieved at the expense of specificity. Although this may result in an increased proportion of false-positive results, it is important in ensuring that all components with true-positive test results are detected and not released. In case of new assays or techniques, precise specifications must be established by testing samples of appropriate populations (e.g. donors, recipients, seroconverted recipients) and by comparing the results generated by the existing test system and by the new one.

Validation of a test system involves four main elements:

- assay reagents which should include quality control material (e.g. positive quality control sample, negative quality control sample, calibrators);
- equipment;
- software, if applicable;
- procedure and handling (test method).

Validation records should not only present proof that the scope and desired specifications are met, but should also provide precise descriptions of all key material, key equipment and conditions of processing (e.g. temperature and time of incubation, rounds per minute in centrifugation). In addition, instructions for handling and processing, by which assay specifications are met, should be put in writing and should be provided with the test system.

Test system specifications that need to be established and/or met by the manufacturer are:

- specificity;
- sensitivity;
- accuracy (degree of closeness of measurements to the true value);
- repeatability (replicates of series);
- reproducibility (replicates of series, variation by operator, by day or by lot of reagents);

- known interferences (e.g. haemolytic sera, lipemic sera);
- lower and upper limits of detection (serial dilution).

Apart from testing appropriate donor/recipient populations, appropriate reference materials should be used to define the performance specifications of a test system. These reference materials should be traceable to the WHO international standard or reference reagents, when available for a specific marker.

The necessary documentation should be available for each test system and should include at least the following information:

- a description of the test system (reagents, controls, devices etc.), equipment and diluents (if applicable);
- safety instructions;
- a description of the assay principle;
- specifications;
- a description of the sampling procedure, sampling plan, sample handling and test procedure;
- internal quality controls (positive and negative), run with every series of donor samples;
- recommended calibration material and calibration frequency (e.g. change of reagent lot);
- primary reading of measurement (format e.g. optical density);
- interpretation of the measurement and/or conversion to result;
- acceptance criteria, cut-off, reference values, limits, pro-zone, grey zone.

Where feasible, the test system should be approved for blood screening by the NRA.

7.4 Assay performance validation

In addition to the validation of the test system by the manufacturer, an on- site validation of the test system in the laboratory is required prior to its use in routine testing. This validation should demonstrate, that:

- the performance specifications of the system established by the kit manufacturer are met by the laboratory;
- laboratory personnel are thoroughly instructed, trained and competent to operate the test system.

Prior to first-time use, critical equipment, including related computer systems, should be thoroughly qualified. Installation qualification, operational qualification and

performance qualification should be carried out and fully documented. This work may involve suppliers and/or third parties. It is strongly recommended that any performance qualification should be performed by the end-user (and not by a third party) since this is intended to demonstrate that the process works as designed.

In addition, a demonstration showing that the test system performance specifications are constantly met in routine donor testing is required. The means by which this may be achieved are:

- inclusion of internal and external quality control materials with every test series;
- previously tested samples collected for use as an internal panel for periodical in-process quality control;
- monitoring measurements of controls (for instance, graphically by using a Levi-Jennings diagram);
- statistically establishing the standard deviation of control measurements;
- implementation of deviation rules (warning range, control range, Westgard rules) to govern corrective actions;
- monitoring trends in control measurements on external standard or reference material;
- successful participation in external quality assessment schemes (proficiency testing) by all qualified members of staff.

8. Management of materials and reagents

8.1 Materials and reagents

Only reagents and materials from approved suppliers that meet documented requirements and specifications should be used. Materials and reagents should meet the legal requirements for medical devices. The management procedures for materials, reagents and supplies should define the specifications for acceptance of any elements that may influence the quality of the final blood component. Receipt logs or records for these critical materials should indicate their acceptability on the basis of the defined specifications and should identify the person accepting them.

8.2 Receipt and quarantine

Appropriate checks (e.g. attached certificates, expiry date, lot number, defects) should be performed on received goods in order to confirm that they correspond to the order and meet the specifications. Damaged containers should be carefully checked to detect possibly affected materials. Incoming critical materials (such as sterile solutions, blood bag systems and testing reagents) should be physically or administratively quarantined

immediately after receipt and until they are released for use. Where the quarantine status is ensured by storage in separate areas, these areas should be clearly marked and their access restricted to authorized personnel. When labels are applied to the containers to indicate their status, the use of different colours may be helpful. Any system replacing physical quarantine (e.g. a computerized system) should provide equivalent security.

8.3 Release of incoming production material and test reagents

Critical material should be received under quarantine and then evaluated for acceptability. After acceptability has been determined, the materials should be released by an authorized person for use in manufacture. The actual release may be performed by an authorized person or under the guidance of a validated computer system. The minimum criteria for the release should be the availability — and check of — certificates or other acceptability records generated by the manufacturer and containing sufficient information to determine product acceptance.

Similarly, each new lot of testing kits should be evaluated by the laboratory to check compliance with predetermined performance standards before release for routine analysis.

The manufacturers of sterile materials (e.g. blood bag systems, anticoagulant solutions) should provide a certificate of release for each batch. The blood establishment should define acceptance criteria for such certificates in writing, and should include at least the name of the material, the manufacturer, compliance with the relevant requirements (e.g. pharmacopoeia or medical device regulations) and confirmation that the materials are sterile and pyrogen-free.

8.4 Storage

Materials and reagents should be stored under the conditions established by the manufacturer and in an orderly manner that permits segregation by batch or lot and stock rotation. Storage and use should follow the “first-expiring first-out” principle (i.e. the material that entered storage first should be used first). The use of the expiry date as an alternative inventory management technique is also acceptable.

Where special storage temperature conditions are required, these should be provided, checked and regularly monitored.

8.5 Traceability of materials and reagents

Inventory records should be kept for traceability. The records should document which batch or lot of materials or reagents have been used for the collection, processing or testing of the blood units or blood components. Inventory of critical supplies such as donation labels with serial numbers should be strictly controlled to avoid mix-ups or mislabelling due to uncontrolled excess labels.

8.6 Supplier/vendor management

All materials and reagents relevant for the quality of the products should be purchased or obtained only from qualified suppliers. The relationship between the two parties (i.e. contract giver and contract acceptor) should be defined in a contract. The blood establishment as contract giver is responsible for assessing the competence of the supplier (contract acceptor).

The contracting process should include:

- a qualification review prior to awarding the contract to ensure that the supplier meets the organizational needs and complies with GMP requirements;
- the setting of appropriate specifications that adequately define the quality of the service or goods;
- appropriate checks on received goods to confirm that they meet specifications;
- checks to ensure that goods in use continue to meet specifications;
- notification of changes to requirements from either party prior to implementing any changes that may affect the quality of the services or goods provided;
- regular contact with suppliers in order to help understand and resolve problems.

9. Manufacturing

9.1 Donor registration

Upon presentation at the blood establishment, donors should positively identify themselves by stating their full name, address and date of birth. Each donor should also provide proof of a permanent place of residence, including a telephone number where appropriate, so that they can be contacted after donation, if necessary.

Proof of identity with a photograph — such as an identity card, passport or driver's licence — should be provided, especially in the case of first-time donors. A careful check of the identity of the donor should be repeated prior to each step that is relevant to the quality of the products and the safety of donors, but at least before donor selection and venipuncture.

If electronic databases are used to maintain donor information, double checks or another validated method to confirm accuracy of information entered manually should be implemented.

9.2 Donor selection

Blood and blood components should be obtained from healthy donors who are carefully selected using a systematic and validated process consisting of review of the donor's health assessment, social behaviour history (the donor questionnaire) and medical examination. This evaluation, along with a review of the results of the infectious disease screening laboratory test, should be used to make sure, prior to the release of any blood component, that the donor presents no increased risk for transmission of infectious agents. NRAs are pivotal in establishing a harmonized framework for donor selection criteria, taking into consideration the types of products, the relevant infectious risks, and the epidemiological data for disease prevalence in the country. The review of these combined data may be used in developing donor selection criteria. The NRA should also be part of any decision-making process intended to modify the donor selection and donation-testing procedures.

Regulatory agencies and professional organizations have respectively published regulations and recommendations on the criteria for the selection of donors of whole blood and blood components (see, for instance, the Council of Europe's *Guide to the preparation, use and quality assurance of blood components*) that can be used as a reference (13). Such guidance documents also explain critical points that should be considered when processing blood and blood components.

Whenever possible, blood donations should be collected through a donation system involving regular and repeat donors. Obtaining blood from regular and repeat donors is a major contribution to ensuring optimal historical medical information about the donors, and therefore to detecting potential risk factors.

9.2.1 Epidemiological surveillance of the donor population

To ensure optimal long-term safety of blood components, blood establishments should maintain continuous epidemiological surveillance of the donor population. The objective of this surveillance is to know, as precisely as possible, the prevalence and incidence, and their respective trends, of infectious markers that are relevant to the safety of blood components. This enables countermeasures to be taken in a timely manner. The system should be able to gather epidemiological data not only at national/regional levels but also among donor populations that provide blood at individual blood establishments within a country or region. Consideration should be given to the travelling patterns of the donor population with respect to possible transmission of infectious diseases (i.e. malaria, Chagas disease, vCJD, etc.).

The information from epidemiological surveillance can furthermore be used:

- to detect, among donor populations of various collection centres, differences that may be associated with objective differences in viral markers within donor populations;

- to detect differences in the donor selection and screening processes at collection centres;
- to detect trends in infectious markers which may reflect either a change in the rate of viral markers in the population or a possible deviation in the donor selection or screening process at specific collection sites;
- to assess the relevance of any preventive measures such as a strengthened donor selection process, additional deferral criteria, or implementation of additional screening tests to avoid contamination of blood components.

When donations from first-time donors are used to prepare blood components, epidemiological data on this specific donor group should be included in the estimate of the risk for infectious diseases transmitted by blood. It has been shown that first-time donors, who may occasionally include test-seeking persons, constitute a group that in some situations is more likely to have bloodborne viral markers than regular donors who have already gone through a selection/deferral process.

It is currently advisable to collect and analyse epidemiological data at the collection sites for HIV1/HIV2, hepatitis C virus (HCV) and hepatitis B virus (HBV) since they historically represent the major pathogenic risks associated with blood components. It is the responsibility of the NRA to define whether this list should be modified or should include additional criteria such as emerging infectious agents, on the basis of local or regional epidemiology. For the current three recommended markers, only confirmed positive tests (i.e. tests which are repeatedly reactive in a screening test and positive in at least one confirmatory test) should be recorded, reported and analysed.

9.2.2 Information to donors

Potential new donors should be informed (ideally both verbally and in writing) that it is necessary to respond to questions about their medical history and personal behaviour so that it can be determined whether they are eligible for blood donation. Written information can be a leaflet explaining infectious risks associated with blood products, and the impact of social behaviour on infectious risks or infectious risk factors. This information is usually provided by a licensed physician, or by a designated qualified person under the direct supervision of a licensed physician. The information should clearly explain the deferral criteria that exclude a donor from donating blood or plasma. It is important to ensure that the reasons for deferral are well understood by the candidate donor.

The candidate donor should be asked to sign a form of informed consent to give blood in which he/she acknowledges understanding the moral and legal responsibilities and possible risks associated with donating blood, as well as the occasional complications that may occur. The declaration of consent should also include a statement that the donor authorizes the release of his/ her blood and blood components for transfusion or further manufacturing.

Donors should be informed to contact the blood establishment if there is an unexpected event after the donation, such as illness or the discovery of new information not disclosed during the health screening.

9.2.3 Questionnaire and interview

The interview assessment of each donor should be carried out by a qualified person who is trained in the use of donor selection criteria using a validated written questionnaire with direct questions if necessary. In order to obtain relevant and consistent information about the donor's medical history (concerning illnesses and drug use) and general health, it is recommended that the donor should review, complete and sign a predefined questionnaire that is adapted to the type of donor (e.g. first-time donor or repeat donor). The questionnaire should cover questions about the medical history of the donor, his/her travel habits, risk behaviours, use of medication, and other medical treatment. A list of countries may be provided to assist the donor to complete the questionnaire with regard to earlier residency or travel. Similarly, a list of drugs that may pose a threat to the recipient or may be an indication of poor donor health may also be provided. The NRA may provide requirements for such lists.

The questions should be drafted in such a way that donors may easily identify whether they are in good health. The questionnaire may be administered in several ways, such as:

- by a person reading questions to the donor and recording the responses;
- by the donor reading the questions and recording the responses;
- by computerized written questions presented to the donor with the donor recording the responses;
- by the computer reading the questions to the donor and the donor recording the responses;
- by other validated methods that ensure that the donor understands the question, how to completely answer the question and how to record the response to the question.

There should be a link between the donor, the donor questionnaire and the collected products. After the donor's history has been reviewed, the collected components should be identified in a way that links the products to the history records but maintains the confidentiality of the donor. The product should be identified by a unique donation number linked to the donor name but the product information should not include the donor name except as required by the NRA in cases such as autologous donations.

After reading the donor information and/or answering the questionnaire, donors who are at risk of carrying a disease transmissible by blood should be able to exclude themselves voluntarily and confidentially. Such confidential self-exclusion

should also be possible after the donation (e.g. by phone). There should be a means of documenting both the reason for self-deferral and the determination of the need for temporary or permanent deferral. These records should be retained in a similar manner to all donor screening records.

Donor identification and information, the donor selection interview and the donor assessment should all take place before each donation. The premises and layout of the blood establishment (or the mobile collection unit) should allow for adequate confidentiality during the donor interview and selection process so as not to discourage the candidate donor from answering questions about personal or private behaviour; otherwise the safety of the blood donation could be compromised.

The minimum intervals between two donations should be defined and should then be audited or reviewed for compliance with the waiting period prior to each donation.

9.2.4 Deferral policy and deferral criteria

As part of the blood establishment's deferral policy, a list of permanent or temporary deferral criteria used for potential donors should be clearly defined, made public, and incorporated in the educational material for donors and the establishment's procedures. It should also be determined whether the donor has previously been deferred, and reasons for any deferral should be reviewed so that a decision may be made on whether to accept the donor for current donation. A donor who is deferred should be informed of the reason for deferral, encouraged not to donate at other facilities while deferred and informed that the reason for the deferral may be shared with other health professionals or government agencies according to NRA recommendations or other legal requirements.

Both acceptance and deferral criteria for the donation of blood should be formulated by the NRA and should be national requirements that are applied nationwide. Within the scope of their role of establishing and implementing effective national regulations, NRAs should enforce such criteria.

Examples of the major permanent deferral criteria found in international guidelines include:

- clinical or laboratory evidence of bloodborne infectious diseases such as acute or chronic infection with HIV, HCV or HBV (in certain jurisdictions donors with elevated titres of anti-HBs may be acceptable);
- past or present intravenous drug use;
- persistent bacterial or protozoal infections.

Other deferral criteria, either permanent or temporary, may include:

- a sexual relationship between men;
- men or women who are engaged in prostitution;
- subjects with haemophilia or other clotting-factor defects;

- sexual partners of any of the above or of someone the donor suspects may carry the above risk factors;
- jaundice within the 12 months prior to donation, since this may be a clinical sign of hepatitis A, B or C;
- transfusion with blood, blood components, plasma products, cellular therapy products or vascularized tissue transplant in the 12 months prior to donation, as blood transfusion and transplantations are risk factors for all bloodborne infections;
- exposure to someone else's blood, including an accidental needle stick in the 12 months prior to donation;
- tattooing, scarification, ear-piercing or acupuncture in the 12 months prior to donation (since these practices may be vehicles for transmission of viral diseases) unless clear evidence is provided that it was carried out under sterile conditions;
- risk factors for Human T-cell lymphotropic virus (HTLV) infection;
- risk factors for malaria infection (e.g. travel in countries where the prevalence is high);
- a confirmed family history of CJD;
- imprisonment longer than three days within the 12 months prior to donation.

When temporary deferral criteria are used, a specific procedure involving trained personnel should be in place for the reinstatement of donors. There are deferral criteria that are temporary (as long as a risk factor has been identified) but that can be waived after additional controls have been carried out on the donor or the period of deferral has passed. NRAs may recommend or define different deferral criteria and timelines, e.g. when implementing NAT testing for the relevant viruses.

9.2.5 Physical examination, donor health criteria and donor acceptance

A targeted physical examination should be carried out by a licensed physician according to an established procedure prior to the first donation and thereafter before subsequent blood donations, and in case of special apheresis programmes at regular intervals. Depending on national regulations established by the NRA, the physical examination may be performed by a suitably educated and trained physician substitute under the supervision of a licensed physician. NRAs should, usually after consultation with the blood establishment, determine the health criteria and the acceptable limits taken into account during the physical examination — such as measurement of haemoglobin, blood pressure, weight, age, pulse rate and temperature, or any other criteria considered to be of concern for the safety of blood components or donors.

A written standard operating procedure based on the relevant acceptance/deferral criteria should be in place at the blood establishment to control donor acceptance and deferral criteria, in compliance with the NRA. Abnormal donor findings should be referred to the physician who has the responsibility of making the final decision about the donor's eligibility on the basis of current medical knowledge and national regulations. If the physician has any doubt about the donor's eligibility, the donor should be deferred.

An appropriate computerized record system (or, if that is not available, a manual system) should be in place for donor records (including their medical history and health status), and for the purpose of ensuring traceability of all donations. Such information provides historical perspective of the health status of donors, including previous temporary deferrals, and contributes to reinforcing the judgement about whether the donation would create a risk to the quality and safety of the blood components.

Records should be kept for each activity associated with the selection of the donor. The record should reflect the decision to accept the donor, taking into consideration the medical history, donor deferral history, the donation interval, the answers given in the interview or questionnaire, and the results of the physical examination. The rejection of a donor and the reason for the deferral should be recorded. An authorized interviewer should sign the donor selection records and the final assessment of the donor's suitability.

As with all other manufacturing steps under GMP, donor selection and acceptability procedures should be followed at all times using the validated methods. Any deviations from established procedures and processes may result in products not meeting specifications so such products should be considered as non-conforming products and must not be released for distribution.

9.3 Collection

9.3.1 Whole blood collection

Donors should confirm their identity (by a method such as stating name and date of birth) immediately prior to venipuncture. Also prior to venipuncture, a check should be made to ensure that the collection system to be used is not damaged or contaminated, and that it is appropriate for the intended collection. Any abnormal moisture or discoloration suggests a defect and in such a case the collection system should be discarded. An investigation should be conducted to evaluate the extent of the problem and appropriate corrective actions should be taken. The collection systems should be used in accordance with the instructions of the manufacturer. Appropriate hand disinfection and personal hygiene procedures should be in place and should be performed by the personnel before each donation.

A standardized and validated procedure for the preparation of the phlebotomy site should be followed using a suitable disinfection solution which should be allowed to dry depending on the type of disinfectant. The expiry date of the disinfectant should be checked. If refillable bottles are used, they should be cleaned before being refilled. The

date of manufacture and the date of opening of in-house disinfectants should be stated on the label. The prepared skin area should not be touched after the disinfection and before the needle has been inserted. Care should be taken not to lean over or speak over the disinfected skin.

For blood donations, laboratory samples should be taken at the time of donation. Procedures should be designed to minimize the risk of microbial contamination to the unit, such as diverting at least the first 10 ml collected in the tubing into test tubes for testing. Methods should be implemented to minimize the deterioration of the sample, such as refrigeration of the sample if required by the manufacturer's instructions for the sample tube or test kit. The sample labelling process should include steps (such as labelling the tubes immediately at the chair side) to prevent the misidentification of samples. The test samples should be labelled immediately in a manner that links the donor, the samples and the blood component without breaching the confidentiality of the donor.

As soon as the collection process starts, good mixing of the blood with the anticoagulant solution should be ensured to avoid risks of activation of the coagulation cascade. The collection bag should be mixed gently at regular intervals thereafter. The mixing can be done by using a continuously running automatic mixing balance or by periodic manual mixing of the unit at least every 90 seconds. Collection of one standard unit of whole blood should be achieved within 12–15 minutes (depending on the component to be prepared later on), as longer durations may result in activation of the coagulation factors and cellular components.

Records should be kept for each activity associated with the donation, including identification of the person who performed the venipuncture. Records should also show any unsuccessful donation, adverse reactions or adverse events.

The maximum collection time for acceptance of the donation for component processing should be specified and controlled. Donations that exceed the maximum time period should be recorded and discarded.

The integral blood bag collection tubing should be sealed off at the end as close as possible to the blood bag and then removed.

A system of unique donation numbers should be used to identify each donor and the related donation, all associated components, samples and records, and to link each one to the others.

When the donation is completed, all records, blood bags and laboratory samples should be checked for the donation number issued. Donation number labels that have not been used should be discarded using a controlled procedure. Procedures to exclude misidentification should be in place. After blood collection, the blood bags should be handled in a way that maintains the quality of the blood (see section 9.4.3.1).

A standard operating procedure should be in place describing the actions to be taken following an unsuccessful donation. It should specify how to handle already labelled material and the circumstances under which a second venipuncture might be possible.

As with other GMP manufacturing steps, the donor product collection process should be followed at all times using the validated methods. Any deviations from these established procedures and processes may result in products not meeting specifications and therefore such products should be considered non-conforming products and should not be released for distribution.

9.3.2 Collection by apheresis

In automated procedures, whole blood is collected from the donor, mixed with anticoagulant, and passed through an automated apheresis device. The blood component of choice is separated from the other blood components which are returned to the donor in a series of collection/separation and return cycles. The operational parameters of the apheresis system should be implemented in compliance with the instructions of the equipment manufacturer and in compliance with any specified safety requirements of the NRA. In general, the anticoagulant — often 4% sodium citrate or anticoagulant citrate dextrose solution A (ACD-A) — is delivered at a rate that will yield a specified ratio of anticoagulant to blood. The volume of the component collected from the donor during one procedure and over a period of time should be regulated by internal policies based on current medical knowledge and on national regulations set by the NRA. The number of collection/separation and return cycles for each donor depends on the total volume of the component that is to be harvested. To determine the number of cycles to be employed, the equipment requires programming with data inputs such as donor weight, height and haemoglobin values, and the pre-donation platelet count if platelets are to be collected. The amount of time required for the donation procedure depends on the number of cycles. An adequately trained physician should be available during apheresis sessions.

The donor apheresis collection process should be followed at all times using validated methods. Any deviations from the established procedures and processes may result in products not meeting specifications and therefore they should be considered non-conforming products and must not be released for distribution.

9.3.3 Safety of donors

All measures should be taken to avoid anything that could adversely affect the donor before, during and after the donation. Special attention should be drawn to the potential risk of transmission of diseases or infections during the collection and sampling processes.

Donors should be given post-donation instructions regarding a period of recovery, such as refraining from certain activities for a while, drinking more fluids than usual and making sure to eat appropriately after the donation. Donors should be advised to refrain from activities such as heavy lifting, operating large items of equipment and other strenuous activities for a period of time until their blood volume has recovered.

Donors should also be provided with information on how to obtain medical advice if they experience an adverse donor reaction after leaving the blood establishment.

Throughout the procedure of withdrawal of blood or blood components, the donor should be monitored. Personnel should be educated to provide appropriate aid in case of any adverse reaction. Donors should be kept under post-donation observation (e.g. for 15 minutes or more) prior to leaving the blood establishment and should be offered refreshment to replace fluid loss. If medically required, drinks may be provided to donors during collection (e.g. apheresis). In these circumstances, a suitable container for the drink is required. Donors should remain under observation for anticipated reactions to donation until they are able to articulate that they feel well enough to leave and be unattended. Immediate care should be given to the donor if there is a donor reaction. Information regarding donor reactions and a process to track and trend reactions should be in place in order to evaluate the number, type and severity of reactions. This information should be used to improve donor safety.

9.4 Component preparation

The quality of the components is assured by control of all stages of manufacture, including donor identification, collection, separation of components, labelling, storage, packaging and dispatch. The standard operating procedures should describe the specifications for materials that will influence the quality of the final blood component. In particular, specifications should be in place for blood and blood components (intermediate and final components), starting materials, additive solutions, primary package material (bags) and equipment.

The standard operating procedures for component preparation should be followed at all times using the validated methods. Any deviations from these established procedures and processes may result in products not meeting specifications and such products should be considered as non-conforming products and must not be released for distribution.

9.4.1 Starting material

The starting materials for preparation of blood components are blood donations collected from suitable donors. Conditions of storage or transport, and the time prior to processing, are contributing factors to the quality of the product. Delays in preparation or unsuitable conditions of storage or transport may adversely affect the quality of the final product. Blood and blood components should be placed in controlled and validated conditions as soon as possible after venipuncture.

Donations and samples should be transported to the processing site in accordance with procedures that ensure both a constant approved temperature and secure confinement. This is especially important when blood is transported from distant collection sites.

Product transport or shipping at appropriate temperatures and temperature monitoring are important to ensure optimal quality. One way to ensure the temperature of products is to use packaging methods validated to keep the blood within the required temperature limits. There should be validation data to demonstrate that the method of transport maintains the blood within the specified temperature range throughout the period of transportation. Alternatively, portable temperature loggers may be used to record the temperature during the transportation of blood to the processing site. Where the blood is not transported by the processing establishment itself, the responsibilities of the transport company should be clearly defined and periodic audits should be conducted to ensure compliance.

9.4.2 Methods of production

Blood components may be prepared by using a centrifugation step with subsequent separation, by using another validated preparation method, or by apheresis technology during collection.

Although the use of closed systems is strongly recommended for all steps in component processing, open systems may exceptionally be necessary due to local constraints in an environment specifically designed to minimize the risk of bacterial contamination. When open systems are used, careful attention should be given to the use of aseptic procedures (12).

Where sterile connecting devices are used to maintain a functionally closed system they should be correctly used in accordance with a validated procedure. The resulting weld should be checked for satisfactory alignment and for validated integrity.

The critical equipment used for the preparation of blood components should be traceable to the corresponding manufacturing records.

9.4.2.1 Centrifugation

The centrifugation parameters (revolutions per minute, temperature, time, acceleration, deceleration) are important for the composition and characteristics of the specific components. These critical parameters should be defined on the basis of validation data that demonstrate a process that consistently produces quality products. For each run, the centrifugation records should identify the operator and confirm that the centrifugation process was performed according to specifications.

9.4.2.2 Separation

After centrifugation, the bag system should be carefully removed from the centrifuge and placed into a plasma expressor or blood separation system. The different layers of the components (red cells, platelets, plasma) should be transferred to the satellite bags within the closed systems, in a manner designed to optimize the harvest of the intended component while minimizing the carry-over of other component fractions.

Alternatively, blood components can be separated during collection by apheresis technology (see section 9.3.2.).

9.4.2.3 Freezing

Freezing is an important processing step that has an impact on quality, especially of plasma. The rate at which freezing proceeds and the core temperature are both considered to be important parameters. Rapid plasma freezing prevents or reduces the loss of critical constituents such as Factor VIII in frozen plasma that is either recovered or obtained by apheresis.

A system should be in place for ensuring that plasma is frozen to the specified core temperature within the time limit, keeping in mind that the freezing speed will be influenced by the type of plasma container, the freezing equipment and the loading pattern, as well as by the volume of plasma. The validation of the freezing process should consider worst-case scenarios that take into account both minimum and maximum loads and positions in the freezer. Recording the temperature of plasma units and the freezing time during a freezing process allows one to evaluate the freezing capacity of the equipment and ensures a standardized freezing process. Validation studies should be available and should demonstrate that the temperature of a frozen pack reaches the proposed storage temperature following the specifications. As indicated above, the aim is to achieve rapid freezing and thereafter to minimize temperature changes to the frozen plasma.

Freezing of cellular components such as red cells or cellular therapy should follow a well defined, validated procedure that ensures the recovery and viability of the intended cellular product during thawing and final preparation steps.

9.4.2.4 Leukocyte reduction

Whole blood may be filtered for leukocyte reduction prior to centrifugation. Filtration of whole blood reduces the level of platelet and leukocyte contamination in plasma and red-cell concentrate preparations. Alternatively, components (e.g. red cells, platelets) may be filtered after separation. The introduction of any leukocyte reduction process either by filtration or special centrifugation technique requires careful validation that takes national requirements into account.

In addition to filter properties, the final result of filtration is influenced by several process parameters (e.g. flow rate, temperature, priming and rinsing) and by the properties of the component to be filtered (e.g. storage history of the component, number of leukocytes and number of platelets). The filtration procedure should incorporate manufacturing specifications such as height and temperature. The method should be fully validated under the conditions to be used. Careful attention should be given to the rate of filtration. Rapid or slow filtration may indicate process failures.

Special centrifugation or filtration techniques of leukocyte reduction are used in several apheresis systems. When a standardized procedure is established on the apheresis system, the method should be validated under the conditions to be used.

An appropriate method should be used for leukocyte counting after leukocyte reduction. The method should be validated to ensure linearity, accuracy and reproducibility.

9.4.2.5 Irradiation

Regular dose-mapping of irradiation equipment should be performed. The exposure time should be set to ensure that all blood and blood components receive the specified recommended minimum dose, with no part receiving more than the maximum recommended dose. The common recommended minimum dose is 25 Gy (2500 cGy).

Care should be taken regarding the increased potassium leakage from red cells after their irradiation, either by limiting the shelf-life of the red-cell concentrate or by further manufacturing steps such as washing.

For the radioactive source, allowance should be made at least annually for source decay. A second independent timing device should be used to monitor exposure time.

Radiation indicators should be used as aids to differentiating between irradiated and non-irradiated blood and blood components. A defined procedure should ensure the separation of components that have not been irradiated from those that have been irradiated, and should ensure they have distinctive labelling.

9.4.3 Blood and blood components

Blood components may be obtained using the methods described in section 9.4.2. However, the sequence and the combination of the methods used in the production of blood components may vary from one product to another.

The collection process itself is already crucial for the quality of blood components. Measures such as a reliable arm-cleaning and disinfection procedure, the use of closed and sterile collection systems, and appropriate microbiological controls should be implemented. Time limits should be defined for the processing of blood components.

There are detailed recommendations concerning the preparation and quality assurance of blood components. See for instance *Guide to the preparation, use and quality assurance of blood components* of the Council of Europe (13). In the following sections, examples of the most important blood components are described. Where NRA requirements exist, they should be followed. Specifications of a number of products are described below.

9.4.3.1 Whole blood

Whole blood for transfusion is blood that is taken from a donor who has been assessed and found suitable as meeting the blood establishment and NRA acceptance criteria. Whole blood is collected in sterile and pyrogen-free containers with a suitable anticoagulant. It may be used without further processing. In some cases, whole blood for transfusion may also be used after leukocyte reduction.

The temperature of whole blood stored for transfusion should remain controlled between 1° and 6°C or in a more stringent range defined by the NRA. The storage time depends on the anticoagulant/preservative solution used.

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent (see 9.6). At a minimum, the following critical parameters should be checked during the quality control assays:

- volume;
- haemoglobin or haematocrit;
- haemolysis at the end of storage.

The primary use of whole blood is as a source material for the preparation of blood components. Transportation and further manufacturing processes should be developed to maximize the number of components that may be produced from a whole blood donation. After collection, whole blood should be kept at a controlled temperature appropriate to the intended component manufacture and should be delivered to the production site as quickly as possible. If whole blood is collected away from the production site, the validated transport systems should ensure that correct temperatures are maintained throughout the process and that the product is delivered within 24 hours. The period between collection and further processing depends on the product but should not exceed 24 hours.

The whole blood may also be filtrated to reduce leukocyte content prior to further processing.

Components should be manufactured by a method validated as meeting the predefined product specifications.

9.4.3.2 Red-cell concentrate

Red-cell concentrates are obtained from whole blood by centrifugation and removal of plasma with or without buffy coat, depending on the centrifugation parameters. After subsequent addition of an appropriate nutrient solution, the red cells should be stored at 1–6°C as soon as possible. Alternatively, red-cell concentrates may be obtained using an apheresis system and likewise stored at 1–6°C. Red-cell units that exceed 10°C after reaching the storage temperature should be discarded. The red-cell concentrate may be used for transfusion without further processing.

To obtain leukocyte-reduced red-cell concentrates, either whole blood filtration can be applied prior to separation or there can be a post-separation filtration of the red-cell concentrate. A fully validated procedure should be established to determine optimum conditions for use of a leukocyte reduction method.

Red-cell concentrates are stored under the same storage conditions as whole blood. The storage time depends on the anticoagulant/preservative solution used.

Further methods of preparation, such as irradiation or washing, are applied to obtain specific red-cell products, depending on the clinical indication.

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent (see 9.6). Parameters measured depend on the type of red-cell concentrate product obtained. At a minimum, the following critical parameters should be checked during the quality control assays:

- volume;
- haemoglobin or haematocrit;
- haemolysis at the end of storage;
- residual leukocytes, if leukocyte reduction is performed.

9.4.3.3 Platelet concentrate

Platelet concentrates are derived from whole blood or are obtained by apheresis.

After collection, whole blood can be kept for up to 24 hours in conditions that are consistent with the preparation of plasma (see section 9.4.3.4.) and validated to maintain a temperature between 20°C and 24°C, following international or NRA recommendations. The whole blood unit is centrifuged so that an optimal number of platelets remain in plasma (platelet-rich plasma, or PRP). Platelet concentrates are then obtained by hard-spin centrifugation of PRP and are then resuspended.

However, if whole blood is centrifuged so that the blood platelets are primarily sedimented to the buffy coat layer, the buffy coat is separated and further processed to obtain a platelet concentrate. Either a single buffy coat or a pool of buffy coats is diluted with plasma or an appropriate nutrient solution, and platelets are concentrated by further centrifugation. The platelet content per unit depends on the method of preparation. Similarly, the residual leukocyte content will vary according to the centrifugation parameters.

Platelet concentrates (both from whole blood and apheresis) should be stored in conditions that guarantee that viability and haemostatic activities are optimally preserved. The storage temperature should be 20–24°C. Continuous gentle agitation of platelets during storage should be sufficient to guarantee the availability of oxygen to the platelets (but should be as gentle as possible). A storage time should be defined in accordance with national regulations set by the NRA; it should normally not exceed five days in the absence of additional measures.

In special circumstances, volume-reduced, split, washed or irradiated platelet concentrates can be prepared for specific treatments.

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent (see 9.6). At a minimum, the following critical parameters should be checked during the quality control assays:

- volume;
- platelet content;

- residual leukocytes, if leukocyte reduction is performed;
- pH, measured at the end of the recommended shelf-life.

9.4.3.4 Plasma for transfusion and Plasma for fractionation

Plasma for transfusion is prepared either from whole blood or from plasma collected by apheresis, and is frozen within a defined period of time to a temperature that should adequately maintain the labile coagulation factors in a functional state, consistent with the intended use of the plasma. In particular, Factor VIII content is critical both as a quality indicator and to assure the efficacy of cryoprecipitate.

If plasma is separated from a unit of whole blood that is refrigerated to 4°C, centrifugation should preferably take place within eight hours of collection (14,15,16).

If the whole blood unit is rapidly cooled to 20–24°C and maintained at this constant temperature after collection, separation can take place within 18– 20 hours because such conditions have been found to protect Factor VIII (17).

If plasma is collected by apheresis, the freezing process should begin as soon as possible, and ideally not later than six hours after the completion of the apheresis process. In compliance with NRA requirements, consideration should be given to the time frames of processing with respect to the anticoagulant and device used and the product to be manufactured.

The freezing process should be validated and should take place in a system that will allow complete freezing to a predefined core temperature in a predefined time (see section 9.4.2.3).

Product stability is dependent on the storage temperature. Storage temperature and shelf-life depend on the intended use of the product. For long-term storage (more than one year) the optimal storage temperature is minus 25°C or colder (18).

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent (see 9.6). At a minimum, the following critical parameters should be checked during the quality control assays:

- volume;
- Factor VIII activity (especially if plasma is used to treat Factor VIII deficiencies);
- residual leukocytes, if leukocyte reduction is performed;
- leakage;
- visual changes.

Virus inactivation and/or quarantine of plasma for transfusion are applied in some countries. Further complementary guidance with respect to virus inactivation is available in *WHO guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products* (2), and in other publications (19,20).

Plasma for transfusion is suitable as source material for the production of fractionated products, and particularly Factor VIII concentrates or other labile factors. Plasma prepared in other ways should meet the specifications of the plasma fractionators and the requirements of the pharmacopoeia and NRA. Further complementary guidance with respect to the production of plasma for fractionation is available in *WHO recommendations for the production, control and regulation of human plasma for fractionation* (3).

9.4.3.5 Cryoprecipitate and Cryo-poor plasma

Cryoprecipitate is the cryoglobulin fraction of plasma and contains a major portion of the Factor VIII, von Willebrand factor, fibrinogen, Factor XIII and fibronectin present in plasma. Cryoprecipitate is obtained from fresh frozen plasma that is prepared in a way that protects Factor VIII stability. Plasma is allowed to thaw either overnight at 2–6°C or by a rapid-thaw technique. Following thawing, the supernatant cryo-poor plasma and the cryoprecipitate are separated by hard-spin centrifugation. The cryo-poor plasma is then expressed into a transfer bag. The two components are refrozen to the appropriate core temperature.

Stability during storage depends on the storage temperature. Storage temperature and shelf-life depend on the intended use of the product. For long-term storage (for two years or longer) the optimal storage temperature is minus 25°C or colder.

Periodic quality control should be performed on the final product to ensure that the manufacturing process is consistent (see 9.6). At a minimum, the following critical parameters should be checked during the quality control assays of cryoprecipitate:

- volume;
- Factor VIII activity;
- clottable fibrinogen;
- von Willebrand factor activity (if applicable).

Virus inactivation and/or quarantine are applied in some countries.

Under certain circumstances the use of small pool preparations of cryoprecipitate (by pooling single-donor cryoprecipitate units) may be desired.

9.5 Laboratory testing

9.5.1 Screening tests for infectious disease markers

9.5.1.1 Testing requirements

The following tests, which are considered mandatory by all regulatory agencies, are relevant to the preparation of blood components and should be performed on each individual blood donation:

- an approved test for Hepatitis B surface antigen (HBsAg);
- an approved test for anti-HIV1/HIV2;
- an approved test for anti-HCV.

All three tests have to be negative. Initially reactive donations should be retested in duplicate by the same assay. Products from a repeatedly reactive donation should not be used for therapeutic applications and should normally be destroyed unless useful for non-therapeutic purposes or investigations. A sample of the donation should be evaluated by a confirmatory test. There should be a system for notifying and counselling the donor if confirmation is positive. It is recommended that national algorithms should be developed and used to enable consistent resolution of discordant/indeterminate or unconfirmed results.

In some countries, additional serological testing is required — for instance, anti-HBc testing may be performed on whole blood donations in order to further reduce the risk of exposure of recipients to HBV by contaminated blood or blood components (3). Additional testing for other agents or markers — such as anti-HTLV I/II, anti-T. cruzi or West Nile Virus (WNV) — may be required by the NRA, taking into account the epidemiological situation in any given region or country or the frequency of donating blood. In addition to testing for immunochemical-serological infectious disease markers, NAT testing of blood donations for the virus genomes has been introduced in some countries to increase the chance of identifying infected donors.

During the natural course of infection, viraemia usually occurs significantly at a point earlier than that at which immunochemical markers (antibodies) can be detected in the infected serum. Thus, infection may be detected by NAT up to 50–60 days before seroconversion (i.e. to HCV) occurs. Testing for the presence of nucleic acid may be performed for viruses such as HCV, HBV, HIV, HAV, WNV (where appropriate) and/or Parvovirus B19, and the application of this technology may be extended to other transmissible microbes. NATs require a particularly sophisticated laboratory environment, special equipment and specially trained laboratory personnel. Mainly because of an extraordinary risk of false-positive results due to the so-called “carry-over” (inadvertent transfer of the amplification product DNA to neat donor samples), very stringent handling and logistics are mandatory.

In contrast to testing for the serological markers of individual donor specimens, NAT testing may be performed following current practices by assembling various samples in mini-pools. However, this requires a thoroughly validated system of sample labelling/identification, a validated strategy and pooling process, and a validated algorithm to resolve pool results to individual donors. Hence, a specific logistics system may have to be established not only in the laboratory but also at the blood establishment in order to collect and suitably label samples. Contiguously tracing samples through the whole process from the donor, through pooling (if applicable), testing and release of the donation may present a particularly demanding challenge.

A system should exist in the country or region for approval of test systems, such as an official approval system by the NRA or a delegated laboratory. The required minimal sensitivity of tests for the different antigens/antibodies or nucleic acids should be defined by the NRA.

9.5.1.2 Handling of samples and data

Multiple specimens may be collected from a donor in order to meet all testing requirements (i.e. ABO typing, viral markers, NAT testing). There should be written standard operating procedures that clearly describe the collection, transportation and labelling of donor samples (i.e. whole blood, sera, anti-coagulant, container tubes etc.) and which define the sampling procedure performed on material for analysis (e.g. how and by whom it is done, transfer of samples, accountability of samples). All screening activities, handling of donor specimens, sampling, analysis and data processing should be separated from patient diagnostic testing (21).

Sample labelling at the site of collection and identification during all subsequent processing is critical and should be under control at all times. Each step of handling and processing should be described, as should the conditions of pre-analytical treatment of specimens (e.g. centrifugation), storage and transportation (duration, temperature, type of container, storage after testing).

Serological testing should be performed on samples transferred directly into the analyser from the original sample tube.

Secondary aliquot samples may be used for NAT testing of mini-pools of individual samples.

The following practical points should be considered in order to ensure the traceability and integrity of samples and data:

- At receipt of specimens at the laboratory, positive identification of those received versus those expected should be performed. The integrity of the sample should be checked for compliance with the recommendations made by the manufacturer of the test kit.
- Aliquot samples for analysis should be withdrawn from the donor sample preferably by automated pipetting equipment.
- To provide for positive identification of all aspects (donation, donor specimen, aliquot samples etc.) it may be advisable to use a barcode system. Hence, starting with the donation, barcodes should be used for labelling. In case of failure of the automatic barcode reader system and/or data processors, an appropriate system should be available for manual entry and tracing of data throughout the whole process until release of donations for transfusion. Manual handling of data should include independent repeat entry into the database; the data format should include a check-digit algorithm or an automated test for identity of the two sets of data.

- Pipetting devices and machines should be validated before routine use, and validation reports should be available.
- Calibration of the pipetting devices should be performed periodically and should be documented.

9.5.1.3 Testing and post-analytical procedures

Testing of blood components should be carried out in accordance with the recommendations of the manufacturer of reagents and test kits. Modifications to the manufacturer's instructions or reagents for donor screening tests should be validated. Where required, prior approval of the NRA should be obtained before the modified method is used for release of a blood component. Laboratory reagents intended for prolonged use should be marked with the preparation date, expiry date, specific storage conditions and signature of the person who prepared them. Instructions for use and storage should be followed.

Screening algorithms should be precisely defined in writing (i.e. standard operating procedures) to deal with initially reactive specimens and to resolve discrepancies in results after retesting. All available measures should be taken to ensure that blood and blood components that are repeat reactive upon screening for an infectious disease marker are excluded from therapeutic use. Repeat reactive material should be stored away from all other blood components in a separate dedicated storage area. Such material should eventually be destroyed to prevent inadvertent re-entry into the transfusion chain.

Test algorithms should provide details for appropriate confirmatory testing. In the case of repeatedly reactive results, clearly defined follow-up instructions should be followed. Actions include:

- notification and deferral of the donor;
- disposal of the indicated donation and of concurrent products;
- tracing and destruction of products which have not yet expired.

If products from the donor have been processed for further manufacture, there should be a procedure in place to assess both the safety of the manufactured products and whether a recall is needed.

Procedures for donor- and/or recipient-initiated look-backs should also be defined. Look-backs should be designed in such a way that the transfusion chain of donor–blood (or blood product)–recipient can be unequivocally reconstructed. The procedure should comprise notification and counselling action where indicated.

The following practical points should be considered in order to ensure that the equipment used for virology testing performs appropriately:

- There should be a mechanism to ensure positive sample identification and linkage to the donor. The preferred method is by sample tubes with barcodes.

- Ideally, the addition of reagent and samples and the testing process should be automated, in order to minimize risk of human errors and to ensure full traceability of the testing process.
- If addition of reagents and samples or preparation of test plates are done manually, full documentation of each addition step should be kept, ensuring identification of the test plate and the location of the reaction well.

9.5.1.4 Test interpretation and follow-up of reactive results

The transfer and interpretation of raw data is a critical step and should therefore be documented and reviewed by a responsible person, as should the test parameters. Traceability and archiving of raw data should be guaranteed (see section 5.2).

The data should be examined by the supervisor, or by another person authorized to do so, before being officially accepted. If computerized systems are used, accepted data should be downloaded directly to the server, or there should be a secure system for manual download which ensures positive release. Manual transcription of results is discouraged as mistakes may be introduced. Acceptance and rejection criteria should be specified.

The following should be given special attention:

- Initial reactive results should be identified by means of a secure and validated system.
- An acceptable system should be in place to confirm repeat reactive results, including sampling, labelling, testing and entry of results.
- Computer algorithms should edit reactive status to repeat reactive, or the editing should be performed by two authorized staff members.
- An appropriate deferral system should exist for repeat reactive results.
- There should be appropriate documentation justifying the re-entry of deferred donors.
- Donors should be informed of the reason for deferral and should be counselled about social behaviours and their status as a future donor.

9.5.2 Blood group typing

Each donation should be tested for ABO and RhD blood groups and at least all first-time donors should be tested for clinically significant irregular red-cell antibodies. When plasma is used for fractionation it should be tested in compliance with the specifications of the fractionator as agreed by the relevant NRA (3).

Testing should be carried out in accordance with the recommendations of the manufacturer of reagents and test kits. Molecular methods may be used to determine blood groups, as necessary.

The ABO and RhD blood group should be verified on each subsequent donation. A comparison should be made with the historically determined blood group. If a discrepancy is found, the applicable blood components should not be released until the discrepancy has been unequivocally resolved.

Donors with a history of transfusions or pregnancy since the last donation should be tested for clinically significant irregular red-cell antibodies. If clinically significant red-cell antibodies are detected, and where applicable, the blood or blood component should be labelled accordingly

NRAs may set different (stronger) requirements.

The ABO/RhD labelling of the red-cell concentrates of all first-time donations should be based on two independent ABO/RhD tests.

9.5.3 Retention samples

As specified by the NRA, an aliquot of the original testing sample should be retained from each donation and stored under conditions recommended by the test manufacturer that would permit retesting if indicated. The procedure for additional testing should be validated to ensure the integrity of the sample (including storage conditions) and the test results. The sample volume, the retention vial, the kind of specimen (serum or plasma), the storage conditions and length of storage should each be defined and should be included in the validation to ensure the integrity of test results.

9.6 Quality monitoring of blood and blood components

Quality control data should demonstrate that critical manufacturing processes are under control. Blood and blood components should comply with specifications and their testing should be performed using test methods approved by the NRA.

All processes — including data transfers and computerized systems — that have an influence on the quality of the products in the area of collection, preparation or testing of blood and blood components should be validated. For critical processes such as rapid freezing of plasma, the need for revalidation should be defined.

Quality control of blood and blood components should be carried out according to a defined sampling plan based on statistical methods. The sampling plan should take into account different collection and production sites, transport, methods of preparation and equipment used. Acceptance criteria should be based on a defined specification for each type of blood component. As an example for fresh frozen plasma, these data may include monitoring of weight/volume, sterility, Factor VIII activity and residual cell counts (platelets, leukocytes, erythrocytes). The sampling plan for testing of blood or blood components should take into account that most components are derived from one donor, and should be considered as a single batch.

Whole blood or blood components should not be released for use if the quality control test indicates that the integrity of the product has been compromised.

The work record should identify the test(s) employed so as to ensure that entries, such as the calculation of results, are available for review.

Test results that do not meet the acceptance criteria should be clearly identified to ensure that blood components of that donation remain in quarantine and that relevant samples are selected for further testing. An investigation should be conducted into the cause of failure prior to additional or repeat testing. Where possible, the performance of the test procedures should be regularly assessed by participation in a formal system of proficiency testing.

Where applicable, the practice of pooling samples before testing should be clearly stated and the donations used in the pooled sample should be recorded. Pooling of samples, such as for the measurement of Factor VIII activity in plasma, is acceptable only where comparative data of pooled samples and individual samples have demonstrated assurance of equivalence.

The results of quality monitoring testing should be subject to periodic review and trend analysis. If the results of quality monitoring suggest that the process is not meeting validated parameters and specifications, then corrective and preventive actions should be taken to correct identified problems before product manufacturing and distribution is continued.

9.7 Labelling

9.7.1 Label information

The collected blood, as well as intermediate and finished blood components, should be labelled with relevant information regarding their identity and release status. The type of label to be used, as well as the labelling methodology, should be established in written standard operating procedures. Whenever possible, machine-readable labels (barcodes) should be used.

The label for a finished blood component should comply with the requirements of the NRA or contain at least the following information:

- the unique donation number (through the use of this number there should be traceability to the donor and all records of the manufacturing steps through to the final product);
- the product name (see section 9.7.2.);
- the required storage conditions;
- the expiry date and, where appropriate, time (see section 9.7.3.);
- the date of collection of the donation(s) from which the blood component was prepared and/or the production date and time (where appropriate);
- the date and time of irradiation (where applicable);
- the ABO and RhD blood group (where appropriate);
- the name or other identification of the component preparation site.

Information regarding the use of the blood product may also be applicable.

For autologous blood components, the label should additionally contain the name and unique identification of the patient as well as the statement “Autologous donation”. In some countries the signature of the donor is also required.

9.7.2 Product name

The name of the blood component should be clearly stated on the label and should indicate any further processing such as leukocyte reduction or irradiation.

In addition, the anticoagulant and/or any nutrient or preservative solution should be mentioned on the label.

9.7.3 Expiry date

Any final blood product should have its expiry date on its label. It should be also kept in mind that certain processing steps, such as irradiation, have an influence on the expiry date so that relabelling becomes necessary.

The definition of an expiry date should be validated and based on scientific data according to the processing steps applied and the storage conditions, or should be the subject of stability studies.

9.8 Release of product

Each blood establishment should be able to demonstrate that a blood component has been evaluated and approved for release by an authorized person, preferably assisted by validated computerized systems. The release criteria and specifications of blood components should be defined, validated, documented and approved by quality assurance. There should be a standard operating procedure that details the actions and criteria that determine whether the blood or blood component can be released. The decision to release the blood components should be made by the responsible person of the establishment; it should be clearly documented and traceability should be ensured. Electronic release of products should be fully validated.

The documented manufacturing processes should be followed at all times using validated methods and procedures. Any deviations from these established procedures and processes may result in products not meeting specifications, in which case they should be considered non-conforming products and must not be released for distribution.

A review of the donor health record, collection and phlebotomy records, consent forms, records of production and test results should be performed and accepted (and should be recorded) prior to the release of the components. The release of products should be arranged in such a way that each component from the donation has been evaluated to ensure conformance with product specifications — such as platelet content in apheresis units, volume in plasma products or appearance for red blood cells — prior

to release for distribution. The decision to release the component should not be made on the basis of a review of the collection processes alone.

There should be a system of administrative and physical quarantine for blood and blood components to ensure that components cannot be released until all mandatory requirements have been met.

In the absence of a computerized system for product status control:

- the label of a blood component should identify the product status and should clearly distinguish released products from non-released (quarantined) ones;
- records should demonstrate that, before a component is released, all current donor health records, collection and phlebotomy records, consent forms and test results have been verified and accepted by an authorized person.

If blood or blood components have been prepared from a donor who has donated on previous occasions, a comparison with previous records — specifically the ABO/RhD and infectious disease marker test results — should be made before final product release to ensure that current records accurately reflect the donor history.

Where release is subject to computer-derived information, the following points should be checked:

- Computer systems should be validated so that they are fully secure against the possibility of blood and blood components which do not fulfil all test or donor selection criteria being released.
- The manual entry of critical data, such as laboratory test results, should require independent verification by a second authorized person.
- There should be a hierarchy of permitted access to enter, amend, read or print data. Methods of preventing unauthorized entry should be in place, such as personal identity codes or passwords which are changed on a regular basis.
- Computer systems should prevent the release of all blood or blood components considered not acceptable for release. It should be possible to prevent the release of any future donation from a donor.

In the event that the final product fails release due to noncompliance with the specified requirements and therefore due to potential impact on recipient safety, all other implicated components should be identified and appropriate action should be taken. A check should be made to ensure that (if relevant) other components from the same donation(s) and components prepared from previous donations given by the donor(s) are identified. There should be an immediate updating of the donor record(s) to ensure that the donor(s) cannot make any further donation, if appropriate.

There should be a defined procedure for the exceptional release of nonstandard blood and blood components under a planned non-conformance system. The decision

to allow such a release should be made by the responsible person; the decision should be clearly documented and traceability should be ensured. Products that cannot be released should be destroyed and the record of destruction should be retained.

9.9 Storage

Standard operating procedures should describe the receipt, handling and storage of material, blood and blood components. There should be a system in place to maintain and control storage conditions, including any transportation that may be required. Autologous blood and blood components should be stored separately. Storage areas for blood components to be dispatched should be located near an entrance or exit to facilitate dispatch and to limit the number of persons entering the main working areas. Only authorized persons should have access to storage areas.

Storage conditions should be controlled, monitored and checked. The personnel authorized should be trained to be aware of the correct storage temperature ranges and alarm settings. Temperature records should be available to demonstrate that the blood components are stored at the required temperature throughout the storage area. A temperature monitoring and recording system that is independent from the temperature regulation system should be in place. Appropriate alarms should be present (upper and lower limits) and regularly checked; the checks should be recorded. Depending on the method of measuring the temperature, a delay of the alarm may be acceptable in order to avoid an alarm being triggered by opening a door or taking out a product, but any such delay should be reasonably justified. If the temperature sensor is placed in a reference solution, no delay of the alarm should be accepted. Appropriate actions on alarms should be defined, and a person should be authorized to decide on the use or rejection of affected products. Temperature excursions may occur and each event should be evaluated using the deviation management system (see section 3.5).

An alternative storage area of appropriate temperature is recommended for recovery in case of temperature control failure of the primary system. Areas for storage should be secured against the entry of unauthorized persons and should be used only for the intended purpose. Storage areas should provide effective segregation of quarantined and released materials or components. There should be a separate area for rejected components and material. If a temporary mechanical or electrical failure affects control of storage temperatures, an examination of the records should be made to evaluate the impact on plasma or blood component quality.

For the main blood components, the common storage temperatures are as follows:

- red-cell concentrate: 1–6°C;
 - plasma for transfusion: minus 25°C or colder;
 - platelets: 20–24°C;
- or in a more stringent range defined by the NRA.

Higher storage temperatures (e.g. minus 20°C) might be acceptable for plasma for transfusion but may result in a significantly shorter shelf-life.

Storage of platelets should also be controlled. Besides the temperature, the continuous agitation is very important. Based on the manufacturer's instructions, the moving velocity should be set in a way that obtains an optimal quality of the product. The moving velocity should be part of the qualification of the equipment.

During the whole collection and manufacturing process it should be ensured that blood or blood components are never placed in direct sunlight or near a heating source.

All storage equipment should be subject to qualification, cleaning and preventive maintenance. Thermometers or temperature sensors should be calibrated annually. The temperature deviation to the standard measuring device should not exceed 1°C.

9.10 Distribution

Prior to distribution, blood components should be visually inspected. There should be a record that identifies the person distributing and the customer receiving the components. Dispatch of blood components should be made by authorized personnel.

At the time of dispatch, there should be a procedure in place to ensure that all blood components being issued have been formally released for use. A standard operating procedure on packaging should be available stating how the contents should be packaged, the materials to be used, and the amount of any cooling elements and their storage conditions before use.

9.11 Shipping

Distribution should take place in a safe and controlled way in order to assure product quality during transport. All transportation and intermediate storage actions, including receipt and distribution, should be defined by written standard operating procedures and specifications.

The shipping containers should be of sturdy construction in order to resist damage and should be validated to maintain acceptable storage conditions for the blood and blood components (e.g. by using appropriate cooling elements or insulation during transport). The transportation and storage conditions for blood components, the packaging format and the responsibilities of the persons involved should be in accordance with standard operating procedures agreed between the sites in question.

9.12 Returns

Blood components should not be returned to stock for subsequent distribution, unless:

- the procedure for return of a blood component is regulated by contract;
- for each returned blood component, it is proven that the agreed storage conditions have consistently been met;

- the integrity of the container has been maintained (i.e. unopened);
- sufficient material is available for compatibility testing.

In case of medical urgency, components may be returned and subsequently distributed using a defined procedure.

The records should indicate that the blood component has been inspected and found to be acceptable before re-issue.

10. Contract manufacturing, analysis and services

In blood establishments, all tasks that have an influence on the quality of collected blood and the manufacture of blood components — such as component processing, testing or information technology support — and which are performed externally by another party, should be subject to a specific written contract. The contract should ensure that the contract acceptor meets GMP requirements in all disciplines relevant to the contract giver's activities.

The contract giver is ultimately responsible for ensuring that processes are in place to assure the control of outsourced activities and the quality of purchased materials. These processes should incorporate QRM and should include:

- assessing (prior to outsourcing operations or selecting material suppliers) the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (e.g. audits, material evaluations, qualification);
- defining the responsibilities and communication processes for quality-related activities of the parties concerned;
- monitoring and review of the performance of the contract acceptor or the quality of the material from the provider, and identification and implementation of any improvements needed;
- monitoring of incoming ingredients and materials to ensure that they are from approved sources using the agreed supply chain.

Details should be specified in a technical quality agreement or contract.

The contract or agreement should:

- clearly establish the duties of each party;
- state the responsibilities of each party;
- mention any technical arrangements;
- define the flow of information, especially regarding deviations and changes;

- define the handling and archiving of documents, samples and other relevant materials and information;
- state that any of the duties given to the contract acceptor should not be passed to a third party without evaluation and approval of the contract giver;
- permit the contract giver and competent authorities to visit and inspect the facilities of the contract acceptor.

The contract giver should provide the contract acceptor with all necessary information to enable compliance with expectations regarding services or goods. This assures that the work or service is performed in compliance with existing regulations. The overall responsibility for the work and duties carried out externally lies always with the contracting company.

The contract should be agreed and signed by quality assurance representatives from both parties and should be kept up to date.

11. Authors and acknowledgements

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America's Blood Centers, Washington DC, USA; Dr V Bogdanova, Federal Medical and Biological Agency (FMBA), Moscow, Russian Federation; Dr T Burnouf, Human Protein Process Sciences, France; Dr M Cheraghali, Dr Amini and Dr Maqsoudloo, Iranian Blood Transfusion Organization, Tehran, Islamic Republic of Iran; Dr JR Cruz, Regional Advisor, WHO, AMRO/ PAHO, Washington, USA; Dr F Darwish, Central Blood Bank, Manama, Kingdom of Bahrain; Dr R Davey, FDA, Rockville, MD, USA; Professor S Diop, National Centre of Blood Transfusion, Dakar, Senegal; Dr D El Sherif, Central Administration of Pharmaceutical Affairs (CAPA), Cairo, Egypt; Dr J Epstein, FDA, Rockville, MD, USA; Dr P Ganz, Health Canada, Ottawa, Canada; Mr A Gould, Medicines Prequalification Programme, WHO, Geneva, Switzerland; Dr I Hamaguchi, National Institute of Infectious Diseases (NIID), Tokyo, Japan; Dr M Heiden, PEI, Langen, Germany; Dr S Hindawi, Blood Transfusion Service, Jeddah, Saudi Arabia; Dr Ho Jung Oh, Korea Food and Drug Administration (KFDA), Seoul, Republic of Korea; Dr M Jutzi, Swissmedic, Bern, Switzerland; Dr H Klein, NIH, Bethesda, MD, USA; Mrs AC Madukwe, National Agency for Food and Drug Administration and Control (NAFDAC), Lagos, Nigeria; Ms GN Mahlangu, Medicines Control Authority, Harare, Zimbabwe; Dr G Michaud, FDA, Rockville, MD, USA; Dr F Moftah, Blood Transfusion Service, Ministry of Health and Population, Agousa, Egypt; Dr Z Mukhtar, National Institute of Health, Islamabad, Pakistan; Dr C Munk and Dr P Strengers, International Society of Blood Transfusion (ISBT), Amsterdam, Netherlands; Dr P Murray, NIH, Bethesda, MD, USA; Dr K Nabae, Ministry of Health, Labour and Welfare, Tokyo, Japan; Dr L Oliva, Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT), Buenos Aires, Argentina; Dr R Perry, International Plasma Fractionation Association (IPFA), Amsterdam, Netherlands; Dr I Prosser, TGA, Canberra, Australia; Dr I Sainte-Marie, AFSSAPS, Paris, France; Professor R Seitz, PEI, Langen, Germany; Dr G Sylvester, European Medicines Agency (EMA), London, UK; Dr G Smith, TGA, Canberra, Australia; Dr D Teo, Blood Services Group, Singapore; Ms A Turner, National Blood Authority, Canberra, Australia; Dr A van Zyl, GMP Inspectorate, WHO, Geneva, Switzerland; Dr I von Hoegen, Plasma Protein Therapeutics Association (PPTA), Brussels, Belgium; Dr T Vuk, Croatian Institute of Transfusion Medicine, Zagreb, Croatia; Dr E Zhiburt, International Society of Blood Transfusion (ISBT), Moscow, Russian Federation; Dr P Zorzi, AFSSAPS, Paris, France.

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3.4 WHO good manufacturing practices for medicinal gases

Annex 5, WHO Technical Report Series, 1044, 2022 (new)

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1. Introduction

- 1.1 Arising from an increased demand for medicinal gases, in particular the use of oxygen in the treatment of patients with coronavirus disease 2019 (COVID-19), the World Health Organization (WHO) Health Products Policy and Standards Department (formerly Essential Medicines and Health Products) and other departments involved in the supply of oxygen and the inspection of production sites of medicinal gases raised the urgency for the preparation of the *WHO good manufacturing practices for medicinal gases guidance text*.
- 1.2 There is an urgent need to scale up the production of medicinal gases, in particular oxygen, meeting the required quality specifications. Where the good manufacturing practices (GMP) standards for medicinal gases are not followed, for example in the production and control of industrial oxygen, the purity and content of oxygen could be affected. The possible contamination of industrial oxygen with viable and non-viable particulate matter, including other impurities, could result in risk to patients when applied for medicinal use. Industrial oxygen should not be used as a medicinal gas.
- 1.3 Although there are other published guidelines, such as those of the European Union and the Pharmaceutical Inspection Co-operation Scheme (PIC/S), the COVID-19 pandemic resulted in an urgent and increased need for the rational use of oxygen and medicinal gases in many WHO Member States.
- 1.4 Whilst the urgent supply of medicinal gases is necessary, appropriate standards should be followed in all countries for the production, control, storage and distribution of oxygen and other medicinal gases to guarantee that gases for medicinal use are of assured quality when they reach the patients.
- 1.5 The recommendations in this guideline are harmonized with the principles of other similar and published guidelines.
- 1.6 WHO GMP guidelines are reviewed and updated regularly, and are available in the WHO Technical Report Series. Manufacturers and distributors of medicinal gases should comply with the relevant parts of WHO GMP guidelines as well as with the content of this document. For ease of reference, a list of some applicable guidelines, such as those reflecting the principles of GMP for active pharmaceutical ingredients (1), the main principles of GMP (2), water for pharmaceutical use (3), data integrity (4), good practices for pharmaceutical quality control laboratories (5), good storage and distribution practices (6), and others (7–15), are referenced below.

2. Scope

- 2.1 This guideline focuses on the production, control, storage and distribution of medicinal gases.
- 2.2 This document does not cover the manufacture of medicinal gases in hospitals or at home for personal use. However, the principles contained in this document may be applied in those instances to ensure that oxygen generated at hospitals or at home is suitable for intended use and meets the appropriate quality standards.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They have been aligned as much as possible with the terminology in related WHO guidelines and good practices and included in the *WHO Quality Assurance of Medicines Terminology Database: list of terms and related guideline*,¹ but may have different meanings in other contexts.

active substance gas. Any gas intended to be an active substance for a medical product or medicinal gas.

air separation. The separation of atmospheric air into its constituent gases.

compressed gas. A gas that, when packaged under pressure for transport, is entirely gaseous at -50°C ; this category includes all gases with a critical temperature less than or equal to -50°C .

container. A cryogenic vessel (tank, tanker or other type of mobile cryogenic vessel), a cylinder, a cylinder bundle or any other package that is in direct contact with a gas.

cryogenic gas. A gas that liquefies at 1.013 bar at temperatures below -150°C .

cylinder. A container, usually cylindrical, suited for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature.

cylinder bundle. An assembly of cylinders that are fastened together, interconnected by a manifold, transported and used as a unit.

evacuate. To remove residual gas from a container or system to a vacuum level of 0.84 bar absolute at sea level using a vacuum system.

¹ https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/mqa-terminology-sept-2020.pdf?sfvrsn=48461fc_5.

gas. Any substance that is completely gaseous at 1.013 bar and +20 °C or has a vapour pressure exceeding 3 bar at +500 °C.

home cryogenic vessel. A mobile cryogenic vessel designed to hold liquid oxygen and dispense gaseous oxygen at a patient's home.

hydrostatic pressure test. A test performed, as required by national or international regulations, in order to ensure that pressure containers are able to withstand pressures up to the container's design pressure.

liquefied gas. A gas that, when packaged for transport, is partially liquid (or solid) at a temperature above –50 °C.

manifold. Equipment or apparatus designed to enable one or more gas containers to be emptied and filled at the same time.

maximum theoretical residual impurity. A gaseous impurity coming from a possible backflow that remains after a cylinder's pretreatment before filling. The calculation of the maximum theoretical residual impurity is only relevant for compressed gases and supposes that these gases act as perfect gases.

medicinal gas. Any gas or mixture of gases classified as a medical product.

minimum pressure retention valve. A cylinder valve that maintains a positive pressure above atmospheric pressure in a gas cylinder after use in order to prevent any internal contamination of the cylinder.

mobile cryogenic vessel. A mobile thermally insulated container designed to maintain the contents in a liquid state.

non-return valve. A valve that permits flow in one direction only.

purge. To remove the residual gas from a container or system by first venting the residual gas from the container or system, then pressurizing the container or system to 2 bar and thereafter venting the gas used for purging to 1.013 bar.

tank. A static thermally insulated container designed for the storage of liquefied or cryogenic gas (also called a fixed cryogenic vessel).

tanker. A thermally insulated container fixed on a vehicle for the transport of liquefied or cryogenic gas.

valve. A device for opening and closing containers.

vent. To remove the residual gas from a container or system down to 1.013 bar by opening the container or system to the atmosphere.

4. Quality management

- 4.1 Companies that are involved in the manufacture, control, storage and distribution of medicinal gases should document, implement and maintain a comprehensively designed and clearly defined quality management system. This is the responsibility of senior management.
- 4.2 Senior management should also assume responsibility for the quality of the medicinal gases manufactured, controlled, released, stored and distributed.
- 4.3 All parts of the quality system should be adequately resourced and maintained.
- 4.4 The quality system should incorporate the principles of good practices (GxP), which should be applied to the life cycle stages of medicinal gases. This includes steps such as the receipt of materials, manufacturing, filling, testing, release, distribution and return of the container after use of a medicinal gas.
- 4.5 The quality system should ensure that:
 - medicinal gases are manufactured, controlled, stored and distributed in accordance with the recommendations in this document and other associated guidelines, such as good-quality control laboratory practices and good storage and distribution practices, where appropriate;
 - managerial roles, responsibilities and authorities are clearly specified in job descriptions;
 - operations and other activities are clearly described in a written form, such as standard operating procedures (SOPs) and work instructions;
 - supplier qualification is carried out and quality agreements are in place;
 - arrangements are made for the supply and use of the correct containers and labels;
 - all necessary controls are in place;
 - there is a system for quality risk management;
 - calibrations and validations are carried out where necessary;
 - the finished product is correctly processed and checked according to the defined procedures and specifications;
 - deviations, suspected product defects, out-of-specification test results and any other non-conformances or incidents are reported, investigated and recorded, and an appropriate level of root cause analysis is applied during such investigations in order to identify the most likely root cause;
 - proposed changes are evaluated and approved prior to implementation, considering regulatory notification and approval where required; after

implementation of any such change, an evaluation should be undertaken to confirm that the quality objectives were achieved and that there was no unintended adverse impact on product quality;

- appropriate corrective and preventive actions are identified and taken where required processes are in place to ensure the management of any outsourced activities that may impact product quality and integrity;
 - finished products are not released and supplied before the authorized person has certified that each production batch has been manufactured and controlled in accordance with product specifications, the recommendations in this document and any other regulations relevant to the production, control and release of these products;
 - there is a system for handling complaints, returns and recalls from the market;
 - there is a system for self-inspection;
 - satisfactory arrangements exist to ensure that medicinal gases are filled, stored, distributed and subsequently handled so that their quality is maintained.
- 4.6 The system for quality risk management should cover a systematic process for the assessment, control, communication and review of risks in the production, filling, control, storage and distribution of medicinal gases and, ultimately, protect the patient from receiving a wrong or contaminated product.

5. Personnel

- 5.1 Personnel involved in the manufacture, control, certification or release of a batch, storage and distribution of medicinal gases should possess qualifications, such as a diploma or degree in, for example, pharmacy, engineering or pharmaceutical sciences, and should have practical experience appropriate for their required duties. They should undergo medical examinations prior to employment and at periodic intervals thereafter, if required by national legislation.
- 5.2 Personnel should receive the appropriate training in relevant guidelines covering GxP and company procedures.
- 5.3 Personnel should be aware of potential hazards and risks to products and patients.
- 5.4 Personnel of outsourced service providers should be appropriately trained, especially where activities could influence the quality of medicinal gases and containers, such as the maintenance and cleaning of cylinders or valves.

6. Documentation

- 6.1 Specifications, SOPs and related documents, as appropriate for the manufacture, control, storage, and distribution of medicinal gases, should be established, implemented and maintained in accordance with the quality management system.
- 6.2 Documents should be designed, prepared, reviewed and distributed with care, in accordance with the quality management system.
- 6.3 Documents should be authorized (approved, signed and dated) by the appropriate responsible persons. No document should be changed without prior authorization and approval.
- 6.4 Documents should have unambiguous content and be laid out in an orderly fashion. The title, nature and purpose should be clearly stated.
- 6.5 Documents should be periodically reviewed and kept up to date.
- 6.6 Superseded documents should not be used.
- 6.7 Where documents require the entry of data, those entries should be clear, legible and indelible, in compliance with good documentation practices and data integrity requirements.
- 6.8 Records should be made or completed when any action is taken and in such a way that all significant activities are traceable. Records should be retained for a period of time as defined by internal procedures or national legislation, as appropriate.
- 6.9 Labels should be clear, unambiguous and in compliance with national or regional legislation, as appropriate (16, 17).
- 6.10 Labels on the cylinders of medicinal gases should contain at least the information as recommended in the pharmacopoeia, where applicable, as well as the following information:
 - the name of the medicinal gas
 - the batch number assigned by the manufacturer
 - the expiry or use-before date, if applicable
 - any special storage conditions or handling precautions that may be necessary
 - directions for use
 - warnings and precautions
 - the name and address of the manufacturer
 - test date (month and year).

6.11 Authorized specifications and testing procedures should be available.

6.12 Records should be maintained for each batch of gas manufactured.

Standard operating procedures and records

6.13 SOPs and associated records should be available for at least:

- equipment
- analytical apparatus and instruments
- maintenance and calibration
- cleaning and sanitization
- personnel matters such as training, clothing and hygiene
- qualification and validation
- self-inspection
- complaints
- recalls
- returns.

6.14 The SOPs for sampling should specify the person or persons authorized to take samples and the sampling instructions.

6.15 The SOPs describing the details of the batch (lot) numbering system should ensure that each batch of medicinal gas is identified with a specific batch number.

6.16 Records of analysis should be maintained.

6.17 Written release and rejection procedures should be available, in particular for the release of the finished product for sale.

6.18 Records should be maintained of the distribution of each batch of medicinal gas.

6.19 Records should be maintained for major and critical equipment, as appropriate, of any qualifications, calibrations, maintenance, cleaning or repair operations, including the dates and the identities of the people who carried out those operations.

7. Complaints

7.1 There should be a written procedure describing the handling of complaints.

7.2 Any complaint concerning a defect of a medicinal gas should be recorded in detail and thoroughly investigated.

- 7.3 Where necessary, the appropriate follow-up action should be taken after the investigation and evaluation of a complaint. Where necessary, a recall of the batch or batches should be considered.
- 7.4 All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
- 7.5 The competent authorities should be informed if a manufacturer is considering action following the identification of serious quality problems with a medicinal gas that may be impacting patients.

8. Recalls

- 8.1 There should be a written, authorized procedure describing the managing of a recall of medicinal gases.
- 8.2 The competent authority of the countries in which a product is recalled or withdrawn from the market should be notified.
- 8.3 The recall of a medicinal gas should be documented. Records should be kept.

9. Returns

- 9.1 There should be a written authorized procedure describing the managing of returns of medicinal gases, which may include inspection or testing.
- 9.2 Once distributed, medicinal gases may only be returned under agreed conditions, as defined by the manufacturer.
- 9.3 Returned medicinal gases should be stored in a controlled manner, in a dedicated area. Returned goods should be clearly identified and kept until a decision is made as to what should be done with the returned goods.
- 9.4 Inventory records of returned medicinal gases should be kept.

10. Self-inspection, quality audits and supplier audits and approvals

- 10.1 Self-inspections should be carried out according to a written, authorized procedure. The objective should be to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions.
- 10.2 Self-inspections should be performed routinely and, in addition, may be performed on special occasions.

10.3 Self-inspections should be done by a team of personnel with knowledge of the manufacture and control of medicinal gases and who are qualified to evaluate compliance with GxP.

10.4 Self-inspections should cover, for example:

- personnel
- premises
- maintenance
- equipment
- production
- quality control
- documentation, including label control
- sanitation and hygiene
- validation and qualification
- calibration
- batch release
- recall procedures
- complaints management
- results of previous self-inspections and any corrective steps taken.

10.5 A report should be made at the completion of a self-inspection.

10.6 Appropriate recommendations for corrective actions should be implemented and an effective follow-up programme should be implemented. The effectiveness of corrective action taken should be verified.

10.7 Self-inspections may be supplemented by a quality audit and conducted by outside or independent specialists. The qualifications of external auditors should be documented.

10.8 Suppliers and contractors should be evaluated before they are approved and included in the approved list. The evaluation should consider a supplier's or contractor's history and the nature of the materials to be supplied or services to be contracted. If an audit is required, it should determine the supplier's or contractor's ability to conform with GMP or the applicable standards.

11. Premises

- 11.1 The premises where medicinal gases are manufactured should be located, designed, constructed and maintained to suit the operations to be carried out.
- 11.2 The layout and design of the premises should aim to minimize the risk of errors, mix ups, contamination and cross-contamination. In addition, it should allow effective cleaning and maintenance without any adverse effect on the quality of the products.
- 11.3 The premises should provide sufficient space for manufacturing, quality control testing and storage operations.
- 11.4 There should be:
 - separate marked areas for different gases;
 - clear identification and segregation of cylinders and mobile cryogenic vessels at various stages of processing (for example, “filled cylinders/mobile cryogenic vessels”, “awaiting checking”, “awaiting filling”, “quarantine”, “certified”, “rejected”, “prepared deliveries”, “empty cylinders/home cryogenic vessels”).

Note: The method used to achieve these various levels of segregation will depend on the nature, extent and complexity of the overall operation. Marked-out floor areas, partitions, barriers, signs, labels or other appropriate means could be used. The segregation of the products may be achieved electronically using a validated electronic system as long as the standards for the cylinders and the vessels intended for medicinal gases are maintained.

- 11.5 Filled cylinders or mobile cryogenic vessels should be stored and transported in a safe manner that ensures that they will be delivered in a clean state, compatible with the environment in which they will be used. Specific storage conditions should be provided as required (for example, for gas mixtures where phase separation occurs upon freezing).

12. Equipment and utilities

- 12.1 Equipment and utilities should be selected, located, constructed and maintained to suit the operations to be carried out.
- 12.2 The layout, design, installation and use of equipment and utilities should aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products.

- 12.3 Equipment should be designed to ensure that the correct gas is filled into the correct container. There should normally be no cross-connections between pipelines carrying different gases. If cross-connections are needed (for example, when filling equipment with mixtures), qualification and controls should ensure that there is no risk of cross-contamination between the different gases. In addition, the manifolds should be equipped with specific connections. These connections may be subject to international or national standards. The use of connections meeting different standards at the same filling site should be carefully controlled, as well as the use of adaptors needed in some situations to bypass the specific fill connection systems.
- 12.4 Tanks and tankers should be dedicated to a single and defined type and quality of gas. Where non-dedicated tanks and tankers are used, risks of contamination should be assessed and controlled, including through the application of the same GxP in the production and having the same quality specification for industrial and medicinal gas.
- 12.5 A common system supplying gas to medicinal and industrial gas manifolds is only acceptable if there is a validated method to prevent backflow from the industrial gas line to the medicinal gas line.
- 12.6 Filling and distribution manifolds should be dedicated to a single medicinal gas or to a given mixture of medicinal gases. In exceptional cases, filling gases used for other gases or other than medical purposes may be acceptable on manifolds dedicated to medicinal gases if justified and performed under control. In these cases, the quality of that gas or mixture of gases should be at least equal to the required quality of the medicinal gas, and GMP standards should be maintained. Filling should then be carried out by campaigns.
- 12.7 Repair, maintenance, cleaning and purging operations of equipment should not adversely affect the quality of the medicinal gases. Procedures should describe the measures to be taken after repair and maintenance operations involving breaches of the system's integrity. It should be demonstrated that the equipment is free from any contamination that may adversely affect the quality of the finished product before releasing it for use. Records should be maintained.
- 12.8 A procedure should describe the measures to be taken when a tanker is taken back into medicinal gas service, for example, after transporting industrial gas or after a maintenance operation. This should include, for example, a change in service documentation and analytical testing. The methods should be validated.

13. Qualification and validation

- 13.1 The scope and extent of qualification and validation should be determined based on risk management principles.
- 13.2 Risk assessment should be carried out and should cover, for example, the premises, equipment, processing, filling, storage and distribution of medicinal gases.
- 13.3 Authorized procedures, protocols and records should be maintained.

14. Production

- 14.1 The manufacturing of medicinal gases should generally be carried out in closed equipment.

Note: Active substance gases can be prepared by chemical synthesis or be obtained from natural sources followed by purification steps, if necessary (for example, in an air separation plant). Where air separation is used to manufacture active substance gases, the manufacturer should ensure that the ambient air is appropriate for the established process. Changes in ambient air quality should be documented and evaluated.

- 14.2 Controls should be identified and implemented to exclude the risks of contamination.
- 14.3 Manufacturing data and information should be included in the records for each batch of cylinders or mobile cryogenic vessels produced.
- 14.4 Records should be maintained for each batch of gas manufactured. These records should include relevant information, as appropriate, such as the following:

- name of the product;
- batch number;
- identification of the person or persons carrying out each significant step;
- equipment used (such as filling manifold);
- quantity of cylinders or mobile cryogenic vessels before filling, including individual identification references and water capacity;
- prefilling operations performed;
- key parameters that are needed to ensure correct fill at standard conditions;
- results of appropriate checks to ensure the containers have been filled;

- specification of the finished product and the results of quality control tests (including reference to the calibration status of the test equipment);
 - quantity of rejected cylinders or mobile cryogenic vessels with individual identification references and reasons for rejection;
 - details of any problems or unusual events and signed authorization for any deviation from instructions;
 - batch label, where applicable;
 - specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment) by the responsible person, with date and signature;
 - batch quantity;
 - date of testing and certification statement;
 - identification reference for the tank (tanker) in which the batch is certified;
 - reference to the supplying tanker (tank), reference to the source gas, as applicable.
- 14.5 Each filled cylinder should be traceable to significant aspects of the production and filling operations.
- 14.6 Cylinders and mobile cryogenic vessels should be checked, prepared, filled and stored in a manner that will prevent mix-ups. Controls should be appropriate and may include labelling, colour coding, signage or separate areas to facilitate segregation of industrial and medicinal cylinders and vessels.
- 14.7 There should be no exchange of cylinders or mobile cryogenic vessels used for medicinal and industrial gases in or from these areas, unless all comply with the specifications of medicinal gases and the manufacturing operations are performed according to GMP standards.
- 14.8 Production through a continuous process, such as air separation, should be continuously monitored for quality. The results of this monitoring should be kept in a manner permitting trend evaluation.
- 14.9 The transfer and delivery of active substance gases in bulk should comply with the same requirements as those for medicinal gases.
- 14.10 The filling of active substance gases into cylinders or into mobile cryogenic vessels should comply with the same requirements as those for medicinal gases.
- 14.11 Requirements applying to cylinders should also apply to cylinder bundles (except storage and transportation under cover).

14.12 Records should be maintained for each batch of gas transferred to tankers. These records should include relevant information, as appropriate, such as the following:

- name of the product;
- batch number;
- identification reference for the tank (tanker) in which the batch is certified;
- date and time of the filling operation;
- identification of the person or persons carrying out the filling of the tank (tanker);
- identification of the person or persons carrying out each significant step (such as line clearance, receipt, preparation before filling, filling);
- reference to the supplying tank (tanker) and reference to the source gas, as applicable;
- relevant details concerning the filling operation;
- equipment used (such as filling manifold);
- prefilling operations performed;
- key parameters that are needed to ensure correct fill at standard conditions;
- a sample of the batch label;
- specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment);
- details of any problems or unusual events, and signed authorization for any deviation from filling instructions;
- certification statement by the authorized responsible person, with date and signature.

Transfer and delivery of cryogenic and liquefied gas

14.13 The transfer of cryogenic or liquefied gases from primary storage, including controls before transfer, should be in accordance with validated procedures designed to avoid any contamination. Transfer lines should be equipped with non-return valves or suitable alternatives. Flexible connections and coupling hoses and connectors should be flushed with the relevant gas before use.

14.14 The transfer hoses used to fill tanks and tankers should be equipped with product-specific connections. The use of adaptors allowing the connection of tanks and tankers not dedicated to the same gases should be adequately controlled.

14.15 Delivery of gas may be added to tanks containing the same quality of gas, provided that a sample is tested to ensure that the quality of the delivered gas is acceptable. This sample may be taken from the gas to be delivered or from the receiving tank after delivery.

Filling and labelling of cylinders and mobile cryogenic vessels

14.16 Before filling cylinders and mobile cryogenic vessels, a batch or batches of gas or gases should be determined, controlled according to specifications, and approved for filling.

14.17 In the case of continuous processes, adequate in-process controls should be performed to ensure that the gas complies with specifications.

14.18 Cylinders, mobile cryogenic vessels and valves should conform with appropriate technical specifications and any relevant requirements by the applicable regulatory authorities. They should be dedicated to a single medicinal gas or to a given mixture of medicinal gases.

14.19 Cylinders should be colour coded according to relevant standards. They should preferably be fitted with minimum pressure retention valves unless other controls are in place to ensure the quality and integrity of the medicinal gas.

14.20 Cylinders, mobile cryogenic vessels and valves should be checked before first use in production and should be properly maintained.

14.21 Checks and maintenance operations should not affect the quality and the safety of the medicinal gas. The water used for the hydrostatic pressure testing carried out on cylinders should be at least of drinking quality.

14.22 As part of the checks and maintenance operations, cylinders should be subject to an internal visual inspection before fitting the valve to make sure they are not contaminated with water or other contaminants.

14.23 An internal visual inspection should be done:

- when cylinders, mobile cryogenic vessels and valves are new and initially put into medicinal gas service;
- following any hydrostatic statutory pressure test or equivalent test where the valve is removed;
- whenever the valve is replaced.

Note: After fitting, the valve should be kept closed to prevent any contaminant from entering the cylinder.

- 14.24 The maintenance and repair operations of cylinders, mobile cryogenic vessels and valves are the responsibility of the manufacturer of the medical product. If subcontracted, they should only be carried out by approved subcontractors, and contracts, including technical agreements, should be established. Subcontractors should be audited to ensure that the appropriate standards are maintained.
- 14.25 Where possible, a system should be implemented to ensure the traceability of cylinders and mobile cryogenic vessels.
- 14.26 Checks to be performed before filling should be done in accordance with an authorized procedure. The following checks should be observed:
- in the case of cylinders fitted with a minimum pressure retention valve, for a positive residual pressure in each cylinder;
 - in the case of cylinders that are not fitted with a minimum pressure retention valve, to make sure it is not contaminated with water or other contaminants;
 - ensuring that all previous batch labels have been removed;
 - the removal and replacement of damaged product labels;
 - a visual external inspection of each cylinder, mobile cryogenic vessel and valve for dents, arc burns, debris, other damage, or contamination with oil or grease; cleaning should be done if necessary;
 - on each cylinder or mobile cryogenic vessel outlet connection to determine that it is the proper type for the particular gas involved;
 - for the date of the next test to be performed on the valve (in the case of valves that need to be periodically tested);
 - on cylinders or mobile cryogenic vessels to ensure that any tests required by national or international regulations (such as hydrostatic pressure test or equivalent for cylinders) have been conducted and are still valid;
 - ensuring that each cylinder is labelled as required.
- 14.27 A batch should be defined for filling operations.
- 14.28 Cylinders and mobile cryogenic vessels that have been returned for refilling should be prepared with care in order to minimize risk of contamination. These procedures, which should include evacuation or purging operations, should be validated.
- 14.29 There should be appropriate checks to ensure that each cylinder or mobile cryogenic vessel has been properly filled.
- 14.30 Each filled cylinder should be tested for leaks using an appropriate method prior to fitting the tamper-resistant seal or device. The test method should not

introduce any contaminant into the valve outlet and, if applicable, should be performed after any quality sample is taken.

- 14.31 After filling, cylinder valves should be fitted with covers to protect the outlets from contamination. Cryogenic vessels should be fitted with tamper-resistant devices.
- 14.32 Each cylinder or mobile cryogenic vessel should be labelled. Patient information leaflets can be made available electronically.
- 14.33 In the case of medicinal gases produced by mixing two or more different gases (in line before filling or directly into the cylinders), the mixing process should be validated to ensure that the gases are properly mixed in every cylinder and that the mixture is homogeneous.

15. Quality control

- 15.1 Each batch of medicinal gas (cylinders, mobile cryogenic vessels, tanks) should be tested in accordance with the marketing authorization, authorized specification or pharmacopoeia and a record of analysis should be maintained, for example a certificate of analysis.

Sampling

- 15.2 There should be an authorized sampling procedure with a sampling plan for testing medicinal gases.
- 15.3 In the case of a single medicinal gas:
 - filled via a multicylinder manifold, the gas from at least one cylinder from each manifold filling cycle should be tested for identity, strength and purity each time the cylinders are changed on the manifold;
 - filled into cylinders one at a time, the gas from at least one cylinder of each uninterrupted filling cycle should be tested for identity, strength and purity.

Note: An example of an uninterrupted filling cycle is one shift's production using the same personnel, equipment and batch of gas to be filled.

- 15.4 In the case of a medicinal gas produced by mixing two or more gases in a cylinder from the same manifold, the gas from every cylinder should be tested for identity, strength and purity of each component.
- 15.5 For excipients, if any, testing on identity could be performed on one cylinder per manifold filling cycle (or per uninterrupted filling cycle in the case of cylinders filled one at a time). Fewer cylinders may be tested in the case of a validated automated filling system.

- 15.6 Premixed gases should follow the same principles as single gases when a continuous in-line testing of the mixture to be filled is performed. Premixed gases should follow the same principle as medicinal gases produced by mixing gases in the cylinders when there is no continuous in-line testing of the mixture to be filled.
- 15.7 The testing for water content should be performed, where required (note the requirements in the pharmacopoeia and as specified by the national regulatory authority).
- 15.8 Other sampling and testing procedures that provide at least an equivalent level of quality assurance may be justified.
- 15.9 Final testing on mobile cryogenic vessels should include a test for assay and identity on each vessel, unless otherwise authorized by the medicines regulatory authority. Testing by batches should only be carried out if it has been demonstrated that the critical attributes of the gas remaining in each vessel before refilling have been maintained.

Note: Where mobile cryogenic vessels are warm or returned from the market with residual product, the gas generated when filling the vessel is sufficient to purge the vessel adequately without any additional purging steps to remove any atmospheric contamination.

- 15.10 Cryogenic vessels retained by customers (hospital tanks or home cryogenic vessels) that are refilled in place from dedicated tankers do not need to be sampled after filling, provided that a certificate of analysis on the contents of the tanker accompanies the delivery.

- 15.11 Records of manual analysis should include at least the following:

- name of the medicinal gas;
- batch number;
- references to the relevant specifications and testing procedures, as approved in the marketing authorization;
- test results and reference to any specifications (limits);
- dates and reference numbers of testing;
- initials of the persons who performed the testing;
- date and initials of the persons who verified the testing and the calculations, where appropriate;
- a clear statement of release or rejection (or other status decision) and the date and signature of the designated responsible person.

15.12 Records of automatic analysis should include at least the following:

- name of the medicinal gas, time and date, and the identity of the person initiating the test. Where access to the sampling and analysis system is controlled, the initials of the person initiating the test may be automatically recorded. The person initiating the test is not required to be part of the quality control department;
- batch number;
- test results, reference to the specification limits and a statement of passed or rejected;
- a clear statement of the change of status of the product being tested.

Note: For automated systems, the person initiating the testing may be the same person responsible for filling the cylinders. Formal approval of the test results may be performed by the responsible person remotely to indicate approval or rejection.

15.13 For bulk medicinal liquid oxygen tankers used for the filling of cryogenic vessels at the customer's premises, the certification and release of batches by the responsible person may be performed retrospectively within a defined time frame, provided the medicinal gas manufacturer can demonstrate that the product being supplied is suitable for patient use.

15.14 Reference and retention samples are not required, unless otherwise specified.

16. Product life cycle and continuous improvement

- 16.1 Manufacturers of medicinal gases should consider adopting a life cycle approach and continuous improvement. These principles should be applied in the relevant areas of the facility, equipment, instrument, utility, product and processes.
- 16.2 A means should be identified for continuous improvement to enable optimizing production and control whilst meeting current demands for supply and satisfying quality requirements of medicinal gases.

17. Storage and distribution

Storage

- 17.1 Precautions should be taken to prevent unauthorized persons from entering storage areas.
- 17.2 Storage areas should be under cover with sufficient capacity to allow the orderly storage of the different medicinal gases. In exceptional cases where this is not

possible, as in the case of bundles of cylinders or large-sized cylinders, the gas outlet should be protected from environmental contamination.

- 17.3 Storage areas should be appropriately designed, constructed and maintained. They should be kept clean and dry and there should be sufficient space and ventilation throughout.
- 17.4 Where special storage conditions are required, these should be provided, controlled, monitored and recorded.
- 17.5 Empty cylinders should be stored separately.
- 17.6 A written cleaning programme should be available indicating the frequency of cleaning and the methods to be used to clean the storage areas.
- 17.7 There should be a written programme for pest control.
- 17.8 Broken or damaged cylinders that can no longer be used should be withdrawn from usable stock and stored separately.
- 17.9 Periodic stock reconciliation should be performed at defined intervals by comparing the actual and recorded stocks. Discrepancies should be identified and investigated. The appropriate corrective action should be taken.

Distribution

- 17.10 Filled gas cylinders and home cryogenic vessels should be handled in such a manner to ensure that they are delivered to customers in a clean and safe state.
- 17.11 Medicinal gases should be transported in accordance with the conditions stated on the labels.
- 17.12 Product, batch and container identity should be maintained at all times. All labels should remain legible.
- 17.13 Distribution records should be sufficiently detailed to allow recall when required.
- 17.14 Appropriately equipped vehicles should be suitable for the transport of medicinal gases, with sufficient space.
- 17.15 Vehicles should be kept clean and maintained.
- 17.16 Defective vehicles and equipment should not be used. These should either be labelled as such or removed from service.
- 17.17 Procedures should be in place for the operation and maintenance of all vehicles and equipment.

- 17.18 There should be written procedures, programmes and records for the cleaning of tankers and vehicles. Agents used should not have any adverse effect on product quality or be a source of contamination.
- 17.19 There should be documented, detailed procedures for the dispatch of medicinal gases. Records for the dispatch should include relevant information to allow traceability. Such records should facilitate the recall of a batch of a medicinal gas whenever necessary.
- 17.20 Tankers and cylinders should be secured to prevent unauthorized access.
- 17.21 Procedures for transport should ensure that:
 - the identity of the medicinal gas is not lost
 - there is no risk of contamination of the medicinal gas
 - precautions are taken against damage and theft
 - environmental conditions are maintained, if required.
- 17.22 The appropriate signs and warnings, where required, should be visible on tankers and vehicles.

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Note: Some parts of the text may have been adapted from other WHO GMP guidelines, as well as those published by the European Union and Pharmaceutical Inspection Co-operation Scheme. The intention is to establish a document that reflects current requirements and is harmonized with those texts. For further details on some of the topics, further reading of original guidelines is recommended.

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3.5 International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceutical products

Annex 2, WHO Technical Report Series, 1025, 2020 (revised)

Acknowledgements

This guideline was prepared by the following experts (in alphabetical order): Mr P.O. Bremer (Norway), Mr C. Fallais (Belgium), Dr S. Kopp (World Health Organization [WHO], Switzerland), Mr P.B. Kulkarni (India), Mr D.V.S. Narasimhan (International Atomic Energy Agency [IAEA], Austria), Mr K.B. Park (Republic of Korea), Dr A. Van Zyl (South Africa), Ms S. Vasanavathana (Thailand) and Mr H. Vera Ruiz (IAEA, Austria).

These guidelines were updated by the following experts (in alphabetical order): Ms Y.M. Chevalme (France), Dr S. Kopp (WHO, Switzerland), Ms A. Korde (IAEA, Austria), Mr S.K. Lyashchenko (United States of America), Mr J.A. Osso Junior (IAEA, Austria), Mr A. Ross (Canada) and Mr S. Todde (Italy).

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1. Scope

This guideline provides a general overview of the minimum good manufacturing practices (GMP) requirements for radiopharmaceutical products. The main principles of GMP are described in detail in the WHO guidelines related to pharmaceutical products (1, 2), as well as in those for sterile pharmaceutical products (3).

The procedures necessary to manufacture, prepare and control radiopharmaceutical products are in large part determined by the nature of these products, the methods of manufacture and their intended use. The recommendations in this guideline are applicable to:

- the production, preparation or compounding of radiopharmaceuticals in hospital radiopharmacies, including diagnostic and therapeutic products;
- the production or compounding of radiopharmaceuticals in centralized radiopharmacies;
- the production or compounding of radiopharmaceuticals in nuclear centres and institutes;
- the production of radiopharmaceuticals by industrial manufacturers; and
- the production of cyclotron-based radiopharmaceuticals.

The scope of this guidance does not include:

- radiopharmaceutical dispensing (i.e. the drawing of a patient's specific unit dose from a bulk vial of a radiopharmaceutical product);
- regulatory authority-approved radiopharmaceutical preparation (i.e. the use of approved kits and approved generators in order to produce a radiopharmaceutical product as per instructions of the marketing authorization holder);
- handling of ready-to-administer radiopharmaceutical products (e.g. receipt, storage, assay, etc.);
- production or compounding of non-radioactive compounds, including cold kits; or
- production of investigational radiopharmaceutical products.

2. Glossary

The definitions given below apply to the terms used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts.

“as low as reasonably achievable”. ALARA is an acronym standing for “as low as reasonably achievable”, used to define the principle of underlying optimization of radiation protection. This is practised based on the principles of time, distance and shielding, as well as an emphasis on creating adequate awareness among all stakeholders.

dispensing. The generation of a patient-specific unit dose, which involves physical withdrawal of the radiopharmaceutical from the bulk single-use or multidose vial into a syringe; dilution with an appropriate diluent as necessary; measurement of the radioactivity content; and labelling of the syringe.

good manufacturing practices for radiopharmaceutical products. Good manufacturing practices (GMP) for radiopharmaceutical products are a set of practices, using a traceable process, that ensure that radiopharmaceutical products are consistently produced and controlled to the quality standards appropriate for their intended use, and designed to consistently yield the radiopharmaceutical product. GMP fall under the umbrella of the overall quality management system (QMS).

manufacturing or production. Within the scope of this guidance, these terms refer to all the operations performed leading up to the finished radiopharmaceutical product, including the purchase of starting materials, production, quality control, release and storage of radiopharmaceuticals.

preparation or kit-reconstitution. Within the scope of this guidance, preparation or kit-reconstitution refers to all the procedures carried out as per instructions from a marketing authorization holder, which involves the addition of radionuclide solution approved by regulatory authorities to an approved cold kit.

primary packaging. Any packaging material that comes into direct contact with the finished radiopharmaceutical product (i.e. an immediate container, such as a vial or a syringe).

quality control. A set of analytical tests designed to demonstrate compliance of the quality of starting materials, intermediates and final radiopharmaceutical products with predetermined specifications for quality acceptance.

quality management system. An appropriate system encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that the radiopharmaceutical product or service will satisfy the given requirements for quality.

radiopharmaceutical compounding. This term refers to producing radiopharmaceuticals with no marketing authorization but pursuant to the order for a specific patient or patients from a physician certified/qualified for practice of nuclear medicine. In various regions of the world, this practice may also be referred to as “in-house preparation”, “in-house-manufacturing” or “hospital preparation”.

radiopharmaceutical product. Any pharmaceutical product that, when ready for use, contains one or more radionuclides (radioactive isotopes) included for medicinal purposes.

secondary packaging. The shielded container housing the primary packaging.

3. Quality management system

- 3.1 There should be a quality management system (QMS) that covers the organizational structure, job descriptions, procedures, processes, resources and actions necessary to ensure adequate confidence that the radiopharmaceutical product or service will consistently yield a product of intended quality.
- 3.2 Principles of risk management should be applied in the establishment, implementation and management of the QMS and GMP.
- 3.3 Risk assessment should include a thorough identification and evaluation of all possible risks associated with the manufacturing process, and controls should be identified in order to minimize those risks to an acceptable level.
- 3.4 Risk assessment and risk controls should be commensurate with the complexity of the risk identified. Because radiopharmaceuticals are significantly different from “traditional” medicines, in both their characteristics and the production process, the GMP requirements applicable to the manufacture of “traditional” pharmaceuticals may often be different from those applied to the manufacture of radiopharmaceutical products.
- 3.5 Radiopharmaceutical-specific characteristics generally include the following:
 - a simple distribution chain, with direct delivery of the finished product from the manufacturer to the nuclear medicine department;
 - a small batch size;
 - a limited shelf-life of minutes to several days; and
 - a quality control (QC) sample representing the entire batch.

In addition:

- diagnostic radiopharmaceuticals often have a low potential to exert pharmacological or toxic effects, owing to the micro-dose levels administered; and
- radiopharmaceuticals are often administered prior to completion of all QC testing. Tests such as sterility and determination of endotoxin content and radionuclidic purity may need to be performed post-release. Hence, the

application of GMP is essential in order to minimize possible risks to the quality that may not be identified through QC pre-release testing.

- 3.6 The risk assessment should cover the unique nature of these agents, with controls that are tailored to the actual production process, the nature of the radiopharmaceutical itself, the level of risk associated and the clinical indication. The preparation and control of these agents should be in compliance with applicable national radiation safety regulations and be based on the principles of ALARA (4, 5) (see Glossary)

4. Qualification and validation

- 4.1 Qualification of instruments and equipment and validation of procedures should be done.
- 4.2 Validation and qualification activities should be planned, organized and documented.
- 4.3 Qualification of premises, utilities, equipment and instruments should demonstrate that they have been designed, installed, operated and performed (as applicable) in accordance with the requirements of GMP and that they are appropriate for their intended use.
- 4.4 The extent of qualification and validation activities should be in accordance with a risk-based approach considering the complexity and critical aspects of the intended radiopharmaceutical production.
- 4.5 A schedule of planned preventive maintenance should be established. Procedures and records should be maintained.
- 4.6 There should be a schedule for regular calibration and verification. Procedures and records should be maintained.
- 4.7 Process validation should be carried out after all other qualification and validation have been successfully completed.
- 4.8 Process validation should be done by including an adequate number of batch preparations, or batches of preparations, of the intended radiopharmaceutical(s), following the same procedures, covering the intended range of batch size and with the same production and quality specifications as typically intended routine batches. The number of batches and the range of batch size should be predetermined as part of a risk assessment performed prior to process validation.
- 4.9 Cleaning validation should be especially focused on surfaces that come into direct contact with the operators or with starting materials, intermediates and finished products.

- 4.10 Non-pharmacopoeia analytical procedures should be validated. Compendial analytical procedures should be verified for their suitability under actual conditions. This should be documented and records maintained.
- 4.11 General principles on validation of analytical procedures may be followed (6, 7); however, the unique nature of radioactivity should be considered and specific adaptations should be made, where required (7).
- 4.12 Revalidation of certain processes (e.g. aseptic process simulation) should be performed on a periodic basis, in accordance with a written procedure. Requalification of equipment should be considered when appropriate, for example, in case of significant changes and/or of deviations.
- 4.13 Validation and qualification activities and results obtained, including the responsibilities of personnel, should all be documented. Records should be maintained.
- 4.14 Processes and procedures should be validated, as appropriate.

5. Product complaints

- 5.1 There should be a written procedure for handling and investigating product complaints.
- 5.2 The procedure should describe the actions to be taken in case of a complaint.

6. Product recall

- 6.1 There should be a written procedure to recall a radiopharmaceutical product, when required.
- 6.2 Since the return of radioactive products is generally not practical, the main purpose of recall procedures for radiopharmaceutical products should be to prevent their use rather than an actual return. If necessary, the return of radioactive products should be carried out in accordance with national and, where applicable, international transport regulations (8).

7. Outsourced activities

- 7.1 Contractors should be evaluated and qualified in accordance with a written procedure. Records should be maintained. The responsibilities of each party should be clearly described in a written agreement.

8. Personnel and training

- 8.1 The manufacturing establishment should have an adequate number of personnel to carry out the intended operations.
- 8.2 The responsibilities placed on any individual should not be so extensive as to present an increased risk to the quality of the product.
- 8.3 The manufacturing establishment and its personnel should be under the supervision of a responsible person(s) who has the appropriate qualifications and experience as required by national legislation.
- 8.4 Personnel should have appropriate qualifications, training and experience related to their responsibilities and job description.
- 8.5 Personnel should receive relevant training in GMP, procedural training and training related to the preparation and control of radiopharmaceutical products.
- 8.6 A written training programme should be followed. Topics should also include the handling of radioactive materials and safety. Personnel should take periodic courses and receive training to keep abreast of the latest developments in their fields.
- 8.7 Training and assessment following training should be documented. Records should be maintained.
- 8.8 All personnel handling radioactive materials should be monitored for possible contamination and radiation exposure.
- 8.9 Personnel working in clean areas should observe good personal hygiene. They should report any personal medical condition that may adversely affect products.

9. Premises

- 9.1 Facilities should be located, designed, constructed, adapted and maintained, in order to suit the operations to be carried out. The laboratories for the handling of radioactive materials should be appropriately designed. Consideration should be given to radiation protection, ALARA compliance, a high level of cleanliness and the appropriate controls to minimize possible microbial contamination.
- 9.2 Lighting, heating, ventilation and air-conditioning (HVAC) systems should be designed to maintain an appropriate temperature and relative humidity where required, in order to ensure the appropriate equipment performance, material storage, safety and comfort of personnel.

- 9.3 Facilities should be correctly maintained. Special precautions should be exercised, in order to ensure that facility repairs and maintenance operations do not compromise product quality. There should be adequate space for the operations to be carried out allowing for efficient workflow, effective communication and overall supervision. Facilities should also be designed in a manner that minimizes the risk of entry of insects, pests and vermin.
- 9.4 Interior surfaces (walls, floors and ceilings) should be smooth, impervious and free from cracks. They should not shed particles and should allow for easy cleaning and decontamination.
- 9.5 Drains should be avoided wherever possible, and should not be present in clean rooms. Where drains are required, these should be appropriately designed.
- 9.6 Sinks should be excluded from clean areas.
- 9.7 Pipes and valves should be appropriately marked, designed and located, in order to facilitate cleaning and decontamination. Vent filters should be appropriately controlled.
- 9.8 Technical area (e.g. rooms to access the rear of hot cells) access points should be configured in a way to minimize the entrance of maintenance and technical personnel to the production (clean) areas.
- 9.9 The HVAC system and pressure cascade design for the different areas should be appropriately designed and maintained, in order to minimize the risk of product contamination and to protect personnel from the risks of radiation exposure. The pressure differentials should be controlled, monitored and recorded. Appropriate controls should be put in place to promote the containment of radioactive gases and vapours.
- 9.10 Radioactive gas emissions should be effectively controlled and monitored, in order to minimize the risk of unnecessary radiation exposure to personnel and the surrounding environment. Alarm systems should be in place.
- 9.11 Radioactive gas should be removed through separate air-handling units fitted with the appropriate filters before being exhausted. These should be regularly checked for performance. The recirculation of radioactive contaminated air should not be allowed.
- 9.12 All operations such as the handling, storage and distribution of materials and products, as well as waste disposal, should be performed in compliance with national regulations and guidance.

- 9.13 A dedicated area with the appropriate equipment should be used for the manufacture of any radiopharmaceutical product involving human blood or plasma.
- 9.14 QC laboratories should be separated from production areas.

10. Equipment

- 10.1 Equipment should be appropriately qualified for its intended use. This includes user requirement specifications, design qualification (if applicable), installation qualification, operational qualification and performance qualification. Equipment and devices, as appropriate, should be calibrated and maintained. Consideration should be given to reducing the risk of product contamination, minimizing the risk of staff radiation exposure and optimizing ergonomics, in order to facilitate the operation, maintenance and cleaning of equipment. Records should be retained (9).
- 10.2 Equipment maintenance, qualification and calibration operations should be recorded and the records maintained.
- 10.3 Computerized systems, such as those controlling equipment, should be included in validation.
- 10.4 The dose calibrator (also known as the activity meter) should be qualified using suitable reference standards. If such a reference standard recognized by a national authority is not available, dose-calibrator manufacturer recommendations or published literature may be used when deciding upon the appropriate dial setting.

11. Starting materials

- 11.1 Starting materials of appropriate quality should be used for radiopharmaceutical production. Written procedures for material acceptance should be established for starting materials to be subsequently used in radiopharmaceutical production.
- 11.2 Specifications for starting materials should be established. Specifications should include, for example, the identity, purity or certification of origin (if applicable) and any other parameters or characteristics required in order to make the material suitable for its intended use.
- 11.3 Starting materials should be accepted by performing in-house testing. Where this is not possible, and in lieu of testing, a review of the certificate of analysis supplied by the reliable material manufacturer to confirm compliance with the specification may be acceptable.

- 11.4 The status of materials should be clear. This includes: (i) accepted materials; (ii) quarantined materials; and (iii) rejected materials.
- 11.5 Rejected materials should be securely stored in an area that is separate from other materials.
- 11.6 Waste materials should be disposed of in accordance with the national requirements.

12. Documentation

- 12.1 Good documentation practices should be followed.
- 12.2 Documents should ensure the traceability of radiopharmaceutical production (including the processes and the product).
- 12.3 The processing records of regular production batches must provide a clear and complete account of the manufacturing history of each batch of a radiopharmaceutical product, showing that it has been manufactured, tested, dispensed into containers and delivered in accordance with the applicable standard operating procedures (SOPs).
- 12.4 A controlled system of written SOPs must be created, in order to cover the requirements for major aspects of radiopharmaceutical manufacturing. The SOPs should be approved, signed and dated by the appropriate responsible person(s). No approved SOP document should be changed without an appropriate review, evaluation and approval by the responsible person(s). The SOPs should be reviewed periodically, in order to ensure applicability.
- 12.5 Documentation should be retained for a period appropriate to the nature of the document content.

13. Good practices in production

- 13.1 Access to restricted areas should be by authorized and trained personnel only.
- 13.2 Only the minimum number of personnel required should be present in clean areas.
- 13.3 Processes should be designed to minimize the risk of contamination, cross-contaminations and mix-ups. The following measures may be adopted to minimize these risks:
 - processing and filling in segregated areas;
 - avoiding the manufacture of different products at the same time, either in the same dedicated space or by the same personnel;

- performing decontamination and visual pre-checks of the manufacturing area; and
 - using manufacturing “closed systems”, whenever possible.
- 13.4 The critical aseptic operations, such as final product vial assembly, vial filling or sterility testing, should be carried out under aseptic conditions of a clean area of grade A in grade B background (10).
- 13.5 Both raw materials and final radiopharmaceutical products should be stored under appropriate controlled conditions.
- 13.6 The stability and shelf-life of the finished product should be defined in a written protocol in agreement with the competent authority.
- 13.7 The expiration dates and times for radiopharmaceutical products should be based upon the results of an adequate number of stability studies.

14. Good practices in quality control

- 14.1 A radiopharmaceutical’s final product acceptance criteria, including criteria for release, should be established and documented in a written SOP.
- 14.2 Sampling procedures should consider the nature and characteristics of the material being sampled (e.g. a small batch size and/or its radioactive content), in order to make sure that the samples are representative of the radiopharmaceutical batch.
- 14.3 The QC procedures should be described in written SOPs.
- 14.4 QC samples should be prepared, handled and stored in a way to ensure adequate identification and segregation of the test samples, to avoid mix-ups and cross-contamination.
- 14.5 A final radiopharmaceutical product that fails to meet the acceptance criteria should be rejected and segregated. Such events should be investigated and the investigation outcome and proposed actions documented.
- 14.6 The release of a batch should be performed by a responsible person. Under certain circumstances (e.g. radiopharmaceuticals with an extremely short radioactive half-life and/or shelf-life), a final radiopharmaceutical drug product may need to be released and delivered prior to completion of all final drug product characterization testing. Under these circumstances, a SOP that clearly describes the required release process should be established and documented.
- 14.7 Batch release by the manufacturer should be carried out by a responsible person who is independent of the person carrying out the production and QC.

15. Labelling

- 15.1 Finished radiopharmaceutical products should be clearly labelled.
- 15.2 Whenever possible, a portion of the primary packaging container should be left uncovered, in order to allow for inspection of the contents.
- 15.3 The content of the labels for radiopharmaceutical products should comply with national legislation and international agreements, where applicable.
- 15.4 In the absence of regulatory authority requirements, the following information should be listed on the primary packaging container label:
- the name of the product and batch number;
 - the name of the manufacturer;
 - the amount of activity in SI units;
 - for liquid radiopharmaceuticals, the total activity or the radioactive concentration per millilitre at the calibration date and time, and the volume of liquid;
 - for capsules, the radioactivity of each capsule at the calibration date and time, and the number of capsules in the container;
 - where relevant, the international symbol for radioactivity;
 - the expiration date and time; and
 - cautionary statements, e.g. "Caution: radioactive material".

Note: reporting information about an activity on a primary label may not always be possible, for reasons of radiation protection. In this case, the information may be reported on the secondary packaging label.

- 15.5 In the absence of regulatory authority requirements, the following information may be listed on the secondary packaging container label, in addition to any information listed on the primary packaging:
- the qualitative composition;
 - excipient information;
 - the route of administration;
 - any special storage instructions; and
 - the address of the manufacturer.

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3.6 Guidelines on good manufacturing practices for the manufacture of herbal medicines

Annex 2, WHO Technical Report Series, 1010,
2018

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Introduction

In line with the publication of the revised World Health Organization (WHO) guidelines on *Good manufacturing practices for pharmaceutical products: main principles* (1), supporting and supplementary guidelines were developed to address specific issues connected with the manufacture of certain types of pharmaceutical product. As part of this series, the WHO *Supplementary guidelines for the manufacture of herbal medicinal products* (2) were issued in 1996. The guidelines were also reproduced in the second volume of the WHO compendium on *Quality assurance of pharmaceuticals* (3). Related WHO documents such as *Guidelines for the assessment of herbal medicines* (4), *General guidelines for methodologies on research and evaluation of traditional medicine* (5), *Quality control methods for medicinal plant materials* (6, 7), *Guidelines on good agricultural and collection practices for medicinal plants* (8), *WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues* (9), *WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines* (10) and *WHO guidelines on good herbal processing practices for herbal medicines* (11) were also issued.

WHO's *Good manufacturing practices: main principles for pharmaceutical products* were updated in 2003 (1, 12). Around the turn of the millennium, various product-specific good manufacturing practice (GMP) guidelines covering herbal medicines were developed by a number of WHO Member States, and by the European Union. They covered several issues relevant to the production and quality control of herbal medicines in more detail. For this reason, within the framework of the *WHO Traditional Medicine Strategy: 2000–2005*, revision of the existing supplementary guidelines was considered desirable; this was also endorsed by the WHO Expert Committee on Pharmaceutical Specifications at its meetings in 2002, 2003, 2004 and 2005. WHO's *Good manufacturing practices: main principles for pharmaceutical products* were further updated in 2013 (13).

These new guidelines are intended to complement those provided in *Good manufacturing practices for pharmaceutical products* (1, 13) and should be read in conjunction with the parent guide. The additional standards addressed by the present guidelines should therefore be considered supplementary to the general requirements (13). They relate specifically to the production and control of herbal medicines, in so far as they mainly focus on identifying the critical steps needed to ensure good quality. The emendation of the text was recommended by the Expert Committee on Specifications for Pharmaceutical Preparations at its fifty-second meeting in 2017 to ensure consistency with the current terminology used and to update the references cited.

The supplementary guidelines are intended to provide WHO Member States with general and minimum technical requirements for quality assurance and control in the manufacture of herbal medicines. Each Member State should develop its own national GMP for manufacturing herbal medicines that are appropriate to its particular situation.

These guidelines deal exclusively with herbal medicines. They do not cover combination of herbal materials with animal materials, mineral materials, chemicals and other substances.

General considerations

Unlike conventional pharmaceutical products, which are usually produced from synthetic materials by means of reproducible manufacturing techniques and procedures, herbal medicines are prepared from materials of herbal origin, which are often obtained from varied geographical and/or commercial sources. As a result it may not always be possible to ascertain the conditions to which they may have been subjected. In addition, they may vary in composition and properties. Furthermore, the procedures and techniques used in the manufacture and quality control of herbal medicines are often substantially different from those employed for conventional pharmaceutical products.

Because of the inherent complexity of naturally grown medicinal plants and the often variable nature of cultivated ones, the instances of contamination with toxic medicinal plants and/or plant parts and the large numbers of active ingredients, few of which have been defined, the production and primary processing has a direct influence on the quality of herbal medicines. For this reason, application of GMPs in the manufacture of herbal medicines is an essential tool to assure their quality.

Glossary

Established terms such as batch, bulk, intermediate product, qualification, starting material and validation are used as defined in the *WHO Good manufacturing practices for pharmaceutical products* (1, 13).

The definitions given below apply to the terms as used in these guidelines. These terms and their definitions have been selected and adopted from other WHO documents and guidelines that are widely used by the WHO Member States (1, 2, 4–11). However, they may have different meanings in other contexts.

Note: As a consequence of the various types of “herbal medicines”, the same type of material may be classified, depending on the case, in different ways (for example, powdered plant material may be both *herbal material* and *herbal preparation* or, in a packed form, *herbal medicinal product*).

active ingredients. Constituents with known therapeutic activity, when they have been identified. When it is not possible to identify the active ingredients, the whole herbal medicine may be considered as an active ingredient.

blending. The process of combining materials or different batches to produce a homogeneous intermediate or finished product.

constituents with known therapeutic activity. Substances or groups of substances that are chemically defined and known to contribute to the therapeutic activity of a herbal material or of a preparation.

herbal medicines. These include *herbs* and/or *herbal materials* and/or *herbal preparations* and/or *finished herbal products* in a form suitable for administration to patients (10).

Note: In some countries herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (for example, animal and mineral materials, fungi, algae, lichens, etc.).

Herbs

Herbs include crude plant materials such as leaves, flowers, fruits, seeds, stem wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered (5).

***Herbal materials*¹**

Herbal materials include, in addition to herbs: fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir-baking with honey, alcoholic beverages or other plant materials (5).

Herbal preparations

Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials (5).

Finished herbal products

Finished herbal products consist of one or more herbal preparations made from one or more herbs (i.e. from different herbal preparations made of the same plant as well as herbal preparations from different plants. Products containing different plant materials are called “mixture herbal products”) (10).

Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be “herbal”.

¹ The participants of the third WHO consultation on quality control, held in Hong Kong SAR, China from 4 to 6 September 2017, recommended that latex and exudates can be included.

markers (marker substances). Reference substances that are chemically defined constituents of a herbal material. They may or may not contribute to their therapeutic activity. However, even when they contribute to the therapeutic activity, evidence that they are solely responsible for the material's clinical efficacy may not be available (10).

medicinal plant. Plants (wild or cultivated) used for medicinal purposes.

medicinal plant materials see **herbal materials**

therapeutic activity. Successful prevention, diagnosis and treatment of physical and mental illnesses, improvement of symptoms of illnesses, as well as beneficial alteration or regulation of the physical and mental status of the body and development of a sense of general well-being.

1. Quality assurance in the manufacture of herbal medicines

In addition to the use of modern analytical techniques (especially high- performance thin-layer chromatography (HPTLC), gas chromatography, high-performance liquid chromatography (HPLC), capillary electrophoresis, mass spectrometry (MS) and atomic absorption) to characterize herbal medicines, quality assurance requires the control of starting materials as well as of storage and processing. For this reason, an appropriate quality assurance system should be applied to the manufacture of herbal medicines.

Note: The methods of choice may depend on the country's infrastructure.

2. Good manufacturing practice for herbal medicines

- 2.1 The general principles of GMP are set out in the parent guidelines (13). Cultivation and collection of medicinal plants, as the starting materials for herbal medicines, as well as processing of herbal medicines are covered by other guidelines (8, 11). The first critical step of their production, where the application of GMP starts, should be clearly designated (see subsection 16.1). This is of particular importance for those products that consist solely of comminuted or powdered herbal materials.

3. Sanitation and hygiene

- 3.1 Because of their origin, herbal materials may contain microbiological contaminants. Furthermore, during the course of harvesting and processing, herbal products that may be especially prone to microbiological contamination are produced. To avoid alterations and to reduce contamination in general, a high level of sanitation and hygiene is necessary during manufacture (for guidelines on personal hygiene see section 11, and for those on sanitation see section 12).

- 3.2 Water supply to the manufacturing unit should be monitored, and, if necessary treated appropriately to ensure consistency of quality.
- 3.3 Waste from the manufacturing unit should be disposed of regularly so as to maintain a high standard of hygiene in the manufacturing area. Clearly marked waste bins should be available, emptied and cleaned as needed, but at least daily.

4. Qualification and validation

- 4.1 Qualification of critical equipment, process validation and change control are particularly important in the production of herbal medicines with unknown therapeutically active constituents. In this case, the reproducibility of the production process is the main means for ensuring consistency of quality, efficacy and safety between batches.
- 4.2 The written procedure should specify critical process steps and factors (such as extraction time, temperature and solvent purity) and acceptance criteria, as well as the type of validation to be conducted (for example, retrospective, prospective or concurrent) and the number of process runs.
- 4.3 A formal change control system should be established to evaluate the potential effects of any changes on the quality of the herbal medicines, particularly content of the active ingredients. Scientific judgement should be used to determine which additional testing and validation studies are appropriate to justify a change in a validated process.

5. Complaints

- 5.1 The person responsible for handling complaints and deciding on the measures to be taken to deal with them should have appropriate training and/or experience in the specific features of the quality control of herbal medicines.
- 5.2 There are two types of complaint, product quality complaints and complaints about adverse reactions or events.
- 5.3 Product quality complaints may be caused by problems such as faulty manufacture, product defects or deterioration as well as, particular to herbal medicines, adulteration of the herbal material. These complaints should be recorded in detail and the causes thoroughly investigated (for example, by comparison with the reference samples kept from the same batch). There should also be written procedures to describe the action to be taken.
- 5.4 To address the second type of complaint, reports of any adverse reaction or event should be entered in a separate register in accordance with national and

international requirements. An investigation should be conducted to find out whether the adverse reaction or event is caused by a quality problem and whether such a reaction or event has already been reported in the literature or whether it is a new observation. In either case, complaint records should be reviewed regularly to detect any specific or recurring problems requiring special attention and possible recall of marketed products. The *WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems* deal with specific issues relating to adverse reactions and adverse events following treatment with herbal medicines (14).

- 5.5 The licensing authority should be kept informed of any complaints leading to a recall or restriction on supply and the records should be available for inspection.

6. Product recalls

- 6.1 The product recall procedure depends very much on the national regulations. There should be a standard operating procedure for storage of recalled herbal medicines in a secure segregated area, complying with the requirements specified under subsection 12.1 (Storage areas) while their fate is decided.

7. Contract production and analysis

- 7.1 The contract partner should have adequate premises and equipment for the production of herbal medicines according to GMP. Validated methods should be applied for cleaning the equipment and premises carefully before using them to produce different herbal medicinal, food or cosmetic products. In the case of raw materials used for producing food, it is recommended to require manufacturing departments to be separated from those where the plant raw material will be cut or powdered for use in the preparation of medicines.
- 7.2 Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable on the specific characteristics of herbal medicines, including their production and quality control testing.

8. Self-inspection

- 8.1 At least one member of the self-inspection team should possess a thorough knowledge of herbal medicines.

9. Personnel

- 9.1 General guidance in relation to personnel involved in the manufacture of medicinal products is given in the parent guide (13).

- 9.2 The release of herbal medicines should be authorized by a person who has been trained in the specific features of the processing and quality control of herbal materials, herbal preparations and finished herbal products.
- 9.3 Personnel dealing with the production and quality control of herbal medicines should have adequate training on the specific issues relevant to herbal medicines.

10. Training

- 10.1 The personnel should have adequate training in appropriate fields such as pharmaceutical technology, taxonomic botany, phytochemistry, pharmacognosy, hygiene, microbiology and related subjects (such as traditional use of herbal medicines).
- 10.2 Training records should be maintained and periodic assessments of the effectiveness of training programmes should be made.

11. Personal hygiene

- 11.1 Personnel entrusted with the handling of herbal materials, herbal preparations and finished herbal products should be required to have a high degree of personal hygiene and to have received adequate training in maintaining appropriate standards of hygiene. Personnel with infectious diseases or skin diseases should not work. Written procedures listing the basic hygiene requirements should be made available.
- 11.2 Personnel must be protected from contact with toxic irritants and potentially allergenic plant materials by means of adequate protective clothing. They should wear suitable gloves, caps, masks, work suits and shoes throughout the whole procedure from plant processing to product manufacture.

12. Premises

- 12.1 Premises should be designed, located, constructed, adapted and maintained to suit the operations to be carried out according to GMP (13).
- 12.2 Because of their potential for degradation and infestation with certain pests as well as their sensitivity to microbiological contamination, production, and particularly storage, of herbal materials and herbal preparations assume special importance.

Storage areas

- 12.3 Storage areas should be well organized and tidy. Special attention should be paid to cleanliness and good maintenance. Any accidental spillage should be cleaned up immediately using methods that minimize the risk of cross-contamination of other materials, and should be reported.
- 12.4 The set-up of storage areas depends on the type of materials stored. The areas should be well labelled and materials stored in a such a way as to avoid any risk of cross-contamination. An area should be identified for the quarantine of all incoming herbal materials.
- 12.5 Storage areas should be laid out to permit effective and orderly segregation of the various categories of materials stored, and to allow rotation of stock. Different herbal materials should be stored in separate areas.
- 12.6 To protect the stored material, and reduce the risk of pest attacks, the duration of storage of any herbal material in unpacked form should be kept to a minimum.
- 12.7 Incoming fresh herbal materials should be processed, unless specified otherwise, as soon as possible. If appropriate, they should be stored between 2 °C and 8 °C, whereas frozen materials should be stored below –18 °C.
- 12.8 Where materials are stored in bulk, to reduce the risk of mould formation or fermentation, it is advisable to store them in aerated rooms or containers using natural or mechanical aeration and ventilation. These areas should also be equipped in such a way as to protect against the entry of insects or animals, especially rodents. Effective measures should be taken to limit the spread of animals and microorganisms brought in with the plant material and to prevent cross-contamination.
- 12.9 Herbal materials, even when stored in fibre drums, bags or boxes, should be stored off the floor and suitably spaced to permit cleaning and inspection.
- 12.10 The storage of plants, extracts, tinctures and other preparations may require special conditions of humidity and temperature or protection from light. Appropriate steps should be taken to ensure that these conditions are provided, maintained, monitored and recorded.
- 12.11 Herbal materials, including raw herbal materials, should be kept in a dry area protected from moisture and processed following the principle of “first in, first out” (FIFO).

Production areas

- 12.12 Production areas should comply with the general requirements of GMP (13). As a rule, campaign work in their processing is necessary. However, if feasible, the use of dedicated premises is encouraged. Moreover, the special nature of the production of herbal medicines requires that particular attention be given to processing products that generate dust. When heating or boiling of the materials is necessary, a suitable air exhaust mechanism should be employed to prevent accumulation of fumes and vapours.
- 12.13 To facilitate cleaning and to avoid cross-contamination, adequate precautions should be taken during the sampling, weighing, mixing and processing of medicinal plants, for example, by use of dust extraction and air-handling systems to achieve the desired differential pressure and net airflow.

13. Equipment

- 13.1 Processing of herbal materials may generate dust or material that is susceptible to pest-infestation or microbiological contamination and cross-contamination. Effective cleaning of the equipment is therefore particularly important.
- 13.2 Vacuum or wet-cleaning methods are preferred. If wet-cleaning is done, the equipment should be dried immediately after cleaning to prevent the growth of microorganisms. Cleaning with compressed air and brushes should be avoided if possible and, if used, should be done with care, as these methods increase the risk of product contamination.
- 13.3 Non-wooden equipment should be used unless tradition demands wooden material. Where it is necessary to use traditional equipment (such as wooden implements, clay pots, pallets or hoppers), this should be dedicated, unless otherwise justified. Such equipment should not come into direct contact with chemicals or contaminated material. If the use of wooden equipment is unavoidable, special consideration must be given to its cleaning as wooden materials may retain odours, be easily discoloured and are easily contaminated.

14. Materials

- 14.1 All incoming herbal materials should be quarantined and stored under appropriate conditions that take into account the degradability of herbal materials and herbal preparations.
- 14.2 Only permitted substances should be used for fumigation, and allowable limits for their residues together with specifications for the apparatus used should be set according to the national regulations.

Reference samples and standards

14.3 The reference standard for a herbal medicine may be a botanical sample of the herbal material; a sample of the herbal preparation, for example, extract; or a chemically defined substance, for example, a known active constituent, a marker substance or a known impurity. The reference standard should be of a quality appropriate to its purpose. If the herbal medicine is not described in a recognized pharmacopoeia, a herbarium sample of the flowering or fruiting top of the whole medicinal plant or part of the medicinal plant (for example, if the whole medicinal plant is a tree) should be available. All reference standards should be stored under appropriate conditions to prevent degradation. Their expiry and/or revalidation date should be determined and indicated.

15. Documentation

15.1 The general principles for documentation are set out in the parent guidelines (13).

Specifications

15.2 The specifications for herbal starting materials, for herbal preparations and finished herbal products are primarily intended to define the quality rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring safety and efficacy. Consistent quality for herbal medicines (finished herbal products) can only be assured if the starting herbal materials are defined in a rigorous and detailed manner. In some cases more detailed information may be needed on aspects of collection or agricultural production. For instance, the selection of seeds, conditions of cultivation and harvesting are important in producing herbal medicines of a reproducible quality (8). Their characterization (which also includes a detailed evaluation of the botanical and phytochemical aspects of the medicinal plant, manufacture of the herbal preparation and the finished herbal product) is therefore essential to allow the establishment of specifications that are both comprehensive and relevant.

15.3 For this reason, in addition to the data called for (13), the specifications for herbal materials should as far as possible include, as a minimum, the following information:

15.4 Herbal materials

- The family and botanical name of the plant used according to the binomial system (genus, species, variety and the authority, i.e. the reference to the originator of the classification, for example, Linnaeus). It may also be appropriate to add the vernacular name and the therapeutic use in the country or region of origin of the plant.

- Details of the source of the plant, such as country and/or region of origin (also state and province, if applicable), whether it was cultivated or collected from the wild and, where applicable, method of cultivation, dates and conditions of harvesting (for example, whether there was extreme weather), collection procedures, collection area, and brand, quantity and date of pesticide application, as required by the *WHO Guidelines on good agricultural and collection practices* (8).
- Whether the whole plant or only a part is used. In the latter case, which part of the plant is used and its state, for example, whole or reduced. For dried plant material, the drying system should be specified, if applicable.
- A description of the plant material based on visual (macroscopic) and/or microscopic examination.
- Suitable identity tests including, where appropriate, identification tests (such as thin-layer chromatography (TLC) or other chromatographic fingerprint) for known active ingredients or markers. A reference sample should be available for identification purposes.
- Details of the assay, where appropriate, of active constituents or markers.
- Limit tests such as dry residue of liquids, ash value (total ash, and ash insoluble in hydrochloric acid), water-soluble extractives, moisture/water content and loss on drying (taking into account the presence of essential oils if any).
- Suitable methods for the determination of possible pesticide contamination and the acceptable limits for such contamination in herbal materials or herbal preparations used in the manufacture of herbal medicines.
- Tests for toxic metals and for likely contaminants, foreign materials and adulterants.
- Tests for fungal and/or microbiological contamination, fumigant residues (if applicable), mycotoxins, pest infestations, radioactivity and their acceptable limits.
- Other appropriate tests (for example, particle size, swelling index and residual solvents in herbal preparations and biological fingerprints such as induced fluorescent markers).

15.5 Specifications for starting materials (and also of primary or printed packaging materials) should include, if applicable, reference to a pharmacopoeial monograph.

15.6 If the herbal material for processing does not comply with its quality specifications, the rules that apply for its rejection, and to storage and disposal of the rejected herbal material, should be included.

- 15.7 Starting materials derived from or comprising genetically modified organisms should comply with existing national or international regulations and the label should include this information. Chemical protection of herbal materials should be in accordance with national and/or international regulations (8).
- 15.8 Qualitative and quantitative information on the active ingredients or constituents with known therapeutic activity in herbal materials and herbal preparations should be given as described in subsection 17.5 (Labelling).

15.9 Finished herbal products

- Tests for microbiological contamination and tests for other toxicants.
 - Uniformity of weight (for example, for tablets, single-dose powders, suppositories, capsules and herbal tea in sachets), disintegration time (for tablets, capsules, suppositories and pills), hardness and friability (for example, for uncoated tablets), viscosity (for internal and external fluids), consistency (semisolid preparations), and dissolution (for tablets or capsules), if applicable.
 - Physical appearance such as colour, odour, form, shape, size and texture.
 - Loss on drying, or water content.
 - Identity tests, qualitative determination of relevant constituents of the plants (for example, fingerprint chromatograms).
 - Quantification of relevant active ingredients, if they have been identified, and the analytical methods that are available.
 - Limit tests for residual solvents.
- 15.10 The control tests and specifications for the finished herbal product should be such as to allow the qualitative and quantitative determination of the main active constituents. If the therapeutic activity of constituents is known, these constituents should be indicated in the documentation. If the therapeutic activity of the individual substances is not known (for example, because they are part of a complex mixture), the constituents useful for assessing the quality should be identified as markers. In both cases, the assay (i.e. quantitative determination) specifications should be defined. When the therapeutic activity of the constituents cannot be determined quantitatively, specifications should be based on the determination of markers.
- 15.11 If either the final product or the herbal preparation contains several herbal materials and a quantitative determination of each active ingredient is not feasible, the mixture of several active ingredients may be determined. The need for such a procedure should be justified.

- 15.12 The concept of different acceptance criteria for release versus shelf-life specifications applies only to finished herbal medicines and not to herbal materials and herbal preparations. Adequate retest periods should be established for the latter. Examples where this may be applicable include assay and impurity (degradation product) levels.

15.13 Herbal preparations

The specifications of herbal preparations consist, depending on the preparation in question, of the relevant items of the specifications for herbal materials or for finished herbal products as outlined above

Processing instructions

- 15.14 The processing instructions should describe the operations to be performed on the plant material, such as drying, crushing, milling and sifting. They should also include the duration and, if applicable, temperatures required for the drying process, and the methods to be used to control fragment or particle size. Instructions on removing foreign matter and other unwanted materials should also be given.
- 15.15 The drying conditions chosen should be appropriate to the type of plant material processed. These depend on both the character of the active ingredients (for example, essential oils) and the type of plant part collected (for example, root, leaf or flower). Drying by direct exposure to sunlight, if not specifically contraindicated is possible, but drying on the ground should be avoided. If the plant should be processed fresh, without drying, the reasons and criteria determining the use of fresh material should be stated.
- 15.16 The instructions for the production of processed extracts should specify details of any vehicle or solvent that may be used, the durations and temperatures needed for extraction, and any concentration stages and methods that may be required.
- 15.17 The permissible environmental conditions, for example, temperature, humidity and standard of cleanliness, should be stated.
- 15.18 Any treatment, such as fumigation, used to reduce fungal or microbiological contamination or other infestation, together with methods of determining the extent of such contamination and potential residues, should be documented. Instructions for carrying out these procedures should be available and should include details of the process, tests and allowable limits for residues together with specifications for apparatus used.
- 15.19 Steps in the processes of blending and adjustment to reach defined contents of pharmacologically active constituents should be clearly documented.

15.20 Rules on the disposal of spent herbal material after processing should also be drawn up.

16. Good practices in production

16.1 To ensure not only the quality, but also the safety and efficacy of complex products of biological origin such as herbal medicines, it is essential that the steps in their production are clearly defined.

Selection of the first production step covered by these guidelines

16.2 For medicinal plants – which are either cultivated or collected from the wild, and which may be used in crude form or subjected to simple processing techniques (such as cutting or comminuting) – the first critical step of their production, i.e. where the application of these guidelines starts, should be clearly designated. The rationale for this designation should be stated and documented. Guidance is provided below. However, for processes such as extraction, fermentation and purification, this rationale should be established on a case-by-case basis.

- Collection/cultivation and/or harvesting of medicinal plants should follow other relevant guidance such as the *WHO Guidelines on good agriculture and collection practices (GACP) for medicinal plants* (8) or national guidelines.
- Generally, post-harvest processing including primary cutting is (or should be) covered by GACP. If further comminuting is carried out during the manufacturing process, it should be covered by GMP, or by these supplementary guidelines. If cutting and comminuting considerably reduce the probability of detection of adulteration or mix-up of herbal materials, application of these supplementary guidelines may be extended to encompass these steps.
- When the active ingredient, as defined in the Glossary, consists exclusively of comminuted or powdered herbs, application of these guidelines starts at the physical processing following primary cutting and comminuting, and includes packaging.
- When herbal extracts are used, the principles of these guidelines should apply to any production step following post-harvest processing.
- In the case of finished herbal products manufactured by fermentation, application of GMP should cover any production step following primary cutting and comminuting. Particular attention should be given to the introduction of cells from a cell bank into the fermentation process.

General considerations

- 16.3 Materials should be handled in a way that is not detrimental to the product. On arrival at the processing facility, the herbal material should be promptly unloaded and unpacked. During this operation, the herbal material should not come into direct contact with the soil. Moreover, it should not be exposed directly to the sun (except where this is a specific requirement, for example, for sun-drying) and it should be protected from rain and microbiological contamination.
- 16.4 Attention should be paid to “classification” of clean area requirements taking into account the possible high degree of initial microbial contamination of herbal materials. Classification of premises as applied to sites for the production of other pharmaceutical substances may not be applicable to sites for the processing of herbal materials. Specific and detailed requirements should be developed to cover microbial contamination of equipment, air, surfaces and personnel, and also for rest rooms, utilities, ancillary and supporting systems (for example, water and compressed air).
- 16.5 Care should be taken to choose cleaning methods appropriate to the characteristics of the herbal materials being processed. Washing dried herbal materials with water is generally inappropriate. When it is necessary to clean them, an air duster or air shower should be used. Where immersion of herbal materials in water or other appropriate agents (such as disinfectants) for cleaning is unavoidable (for example, to eliminate suspected coliform bacteria), it should be kept to a minimum.
- 16.6 The presence of plant materials from different species and varieties, or different plant parts should be controlled throughout the entire production process to avoid contamination, unless it is assured that these materials are equivalent.
- 16.7 If time limits are specified in the master production instructions, these limits should not be exceeded, to ensure the quality of intermediates and finished products. The less is known about the constituents responsible for the therapeutic activity, the more strictly this rule should be obeyed. Such time limits, however, may be inappropriate when processing to achieve a target value (for example, drying to a predetermined specification) because completion of processing steps is determined by in-process sampling and testing.

Mixing of batches and blending

- 16.8 Herbal medicines with constituents of known therapeutic activity are often standardized (i.e. adjusted to a defined content of such constituents). The methods used to achieve such standardization should be documented. If another substance is added for these purposes, it is necessary to specify, as a range, the quantity

that may be added. Blending different batches of a specific herbal material (for example, before extraction) or mixing different lots of similar herbal preparations may also be acceptable. Records should be maintained to ensure traceability. The blending process should be adequately controlled and documented and the blended batch should be tested for conformity with established specifications where appropriate.

- 16.9 Batches should be mixed only if homogeneity of the mixture can be guaranteed. Such processes should be well documented.
- 16.10 Out-of-specification batches of herbal medicines should not be blended with other batches for the purpose of meeting specifications, except for standardization of the content of constituents with known pharmaceutical therapeutic effect. Every batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.
- 16.11 Where particular physical attributes of the material are critical, blending operations should be validated to show uniformity of the combined batch. Validation should include testing of critical attributes (for example, particle size distribution, bulk density and tapped density) that may be affected by the blending process.
- 16.12 The expiry date of the blended batch should be chosen according to the date of manufacture of the oldest batch in the blend.

17. Good practices in quality control

17.1 General

- 17.1.1 The personnel of quality control units should have the necessary expertise in herbal medicines to enable them to carry out identification tests and recognize adulteration, the presence of fungal growth or infestations and lack of uniformity in a consignment of herbal materials.
- 17.1.2 The quality control of the herbal material, herbal preparations and finished herbal products should establish their quality but this does not imply the control of every single constituent.

17.2 Sampling

- 17.2.1 Because herbal materials are an aggregate of individual plants and/or different parts of the same plant and thus have an element of heterogeneity, sampling should be carried out with special care by personnel with the necessary expertise.

17.2.2 Further advice on sampling and visual inspection is given in the WHO document *Quality control methods for herbal materials* (7).

17.3 Testing

17.3.1 The identity and quality of herbal material, herbal preparations and of finished herbal products should be tested as described in the *Quality control methods for herbal materials* (7). The minimum requirement for the technical equipment is for instruments to perform the tests described (7). Moreover, each country should develop this basic requirement for technical equipment further, according to the country's needs.

17.3.2 Herbal material, herbal preparations (including extracts) and finished herbal products can be categorized as follows:

- a. the active constituents are identified, and may be quantified as such;
- b. the main group of components that contribute to the activity (i.e. the constituents with known therapeutic activity) are known and can be quantified as a total (for example, essential oils) or calculated using a representative substance belonging to the group (for example, flavonoids);
- c. the former are not identified and/or are not quantifiable, but marker substances are;
- d. others, where quantification (i.e. specification for a certain quantity of a constituent) is not applicable or feasible.

17.3.3 Identification methods may be based on:

- physical and, if applicable, macroscopic (organoleptic) and microscopic tests;
- chromatographic procedures (TLC, HPLC, HPTLC or gas–liquid chromatography (GLC)), spectrometric techniques (ultraviolet-visible (UV-VIS), IR, nuclear magnetic resonance (NMR), MS); and/or;
- chemical reactions.

17.3.4 The identification test methods should be specific for the herbal material, herbal preparation or finished herbal product and ideally should be capable of discriminating between the required herbal material and likely potential substitutes or adulterants. The identification methods used for groups a and b should be capable of detecting the said active ingredients and at least the main ingredients should be stated on the label. For group c, the analytical procedure should be based on characteristic constituents, if any.

- 17.3.5 Reference samples of herbal materials should be made available for use in comparative tests, for example, visual and microscopic examination and chromatography.
- 17.3.6 Quantitative determination of known active components for members of groups a and b and of markers for members of group c is necessary.
- 17.3.7 The development and execution of quality control methods for herbal materials, herbal preparations and the finished herbal products should be in line with subsection 15.1 (Specifications). Tests and quality requirements that are characteristic of the given analyte should be selected.
- 17.3.8 Particularly for herbal materials in group d and for finished herbal products containing such materials, characteristic chromatograms (and/or fingerprint chromatograms) may be applicable. Use of these methods may ensure that the main constituents can be easily tracked throughout the production process. Caution is necessary, however, for every delivery of herbal materials and every batch of herbal preparations (including extracts) will have slightly different chromatograms/fingerprints resulting from differences in chemical compositions caused by intrinsic or extrinsic factors.

17.4 Stability studies

- 17.4.1 If the expiry date for a herbal material or herbal preparation is given, some stability data to support the proposed shelf life under the specified storage conditions should be available. Stability data are always required to support the shelf life proposed for the finished herbal products.
- 17.4.2 Finished herbal products may contain several herbal materials or herbal preparations, and it is often not feasible to determine the stability of each active ingredient. Moreover, because the herbal material, in its entirety, is regarded as the active ingredient, a mere determination of the stability of the constituents with known therapeutic activity will not usually be sufficient. Chromatography allows tracing of changes that may occur during storage of a complex mixture of biologically active substances contained in herbal materials. It should be shown, as far as possible, for example, by comparisons of appropriate characteristic/fingerprint chromatograms, that the identified active ingredient (if any) and other substances present in the herbal material or finished herbal product are likewise stable and that their content as a proportion of the whole remains within the defined limits.
- 17.4.3 The fingerprint methods used for the stability studies should be as similar as possible to those used for quality control purposes.

- 17.4.4 For identified active ingredients, constituents with known therapeutic activity and markers, widely used general methods of assay, and physical and sensory or other appropriate tests may be applied.
- 17.4.5 To determine the shelf life of finished herbal products, strong emphasis should also be placed on other tests mentioned in subsection 15.1 (Specifications), such as moisture content, microbial contamination and general dosage form control tests.
- 17.4.6 The stability of preservatives and stabilizers should be monitored. When these are not used, alternative tests should be done to ensure that the product is self-preserving throughout its shelf life.
- 17.4.7 Samples used for stability studies should be stored in the containers intended for marketing.
- 17.4.8 Normally the first three commercial production batches should be included in the stability-monitoring programme to confirm the expiry date. However, where data from previous studies, including pilot batches, show that the product is expected to remain stable for at least two years, fewer than three batches can be used. The testing frequency depends on the characteristics of the herbal medicinal products and should be determined on a case-by-case basis.
- 17.4.9 The protocol for ongoing stability studies should be documented. This would normally involve one batch per year being included in a stability-monitoring programme.

17.5 Packaging materials and labelling

- 17.5.1 All packaging materials, such as bottles, should be stored properly. Controls on the issue and use of these packaging materials should be adequate to ensure that incorrect labels and cartons are not used.
- 17.5.2 All containers and closures should be thoroughly cleaned and dried before being used to pack the products.
- 17.5.3 There should be adequate information on the label (or the package insert) to inform the users of the composition of the product (in addition to the brand name, if any), indications or actions, directions for use, cautions and adverse reactions, if any, and the expiry date.
- 17.5.4 Finished herbal products may contain several herbal materials and/or herbal preparations. Unless otherwise fully justified, the full quantitative composition of the herbal ingredients should be stated on the product label. If this is not

possible, at least the main ingredients should be stated on the label while the full qualitative composition could appear on the package insert.

17.5.5 The qualitative and quantitative characteristics of the active ingredients in herbal materials and herbal preparations should be expressed in the following ways:

- for herbal materials and herbal preparations consisting of comminuted or powdered herbal materials:
 - a. the quantity of the herbal material must be stated or, if constituents with known therapeutic activity have not been identified, the quantity of the herbal material or herbal preparation should be stated; or
 - b. the quantity of the herbal material or herbal preparation should be given as a range, corresponding to a defined quantity of constituents with known therapeutic activity (see examples).

Examples:

(a)

Name of the active ingredient or active plant material(s)	Quantity of constituent
<i>Valerianae radix</i>	900 mg

(b)

Name of the active ingredient or active herbal material(s)	Quantity of constituent
<i>Sennae folium</i>	415–500 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as sennoside B

- For herbal preparations produced by steps, which go beyond comminution, the nature and concentration of the solvent and the physical state of the extract should be given. Furthermore, the following should be indicated:
 - a. the equivalent quantity or the ratio of a herbal material to herbal preparation must be stated if therapeutic activity of the constituents is unknown (this does not apply to fatty or essential oils); or
 - b. if the therapeutic activity of the constituents is known, the quantity of the herbal preparation may be given as a range, corresponding to a defined quantity of the constituents with known therapeutic activity (see examples).

Examples:

(a)

Name of the active substance or active herbal material(s)	Quantity of constituent
<i>Valerianae radix</i>	25 mg dry ethanolic (96% v/v) extract (8:1) or 125 mg ethanolic (96% v/v) extract, equivalent to 1000 mg of <i>Valerianae radix</i>
other ingredient	
dextrin	20–50 mg

(b)

Name of the active substance or active herbal material(s)	Quantity of constituent
<i>Sennae folium</i>	100–130 mg dry ethanolic (96% v/v) extract (8:1), corresponding to 25 mg of hydroxyanthracene glycosides, calculated as sennoside B
other ingredient	
dextrin	20–50 mg

17.5.6 The composition of any solvent or solvent mixture used and the physical state of the extract should be identified.

17.5.7 If any other substance is added during the manufacture of the herbal preparation to adjust the level of constituents of known therapeutic activity, or for any other purpose, the added substance(s) should be described as such or as “other ingredients” and the genuine extract as the “active ingredient”. However, where different batches of the same extract are used to adjust constituents with known therapeutic activity to a defined content or for any other purpose, the final mixture should be regarded as the genuine extract and listed as the “active ingredient” in the unit formula.

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3.7 WHO good manufacturing practices for pharmaceutical products containing hazardous substances

Annex 3, WHO Technical Report Series, 957,
2010

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1. Introduction

- 1.1 These guidelines set out good practices applicable to facilities handling pharmaceutical products (including active pharmaceutical ingredients (APIs)) that contain hazardous substances such as certain hormones, steroids or cytotoxins. They do not replace national legislation for protection of the environment and personnel. Other WHO guides to good manufacturing practices (GMP) and regulations need to be observed in addition to the workers' safety criteria (1–4).
- 1.2 These guidelines are to be read in conjunction with other WHO GMP guidelines with respect to building finishes and general services installations, among others. See the reference list for relevant publications which serve as additional background material. The primary focus of these guidelines is on the air-conditioning and ventilation systems of the facility; however, the document also provides some guidance on personnel protection.
- 1.3 The areas to which this document applies include all zones where the handling of products could lead to cross-contamination, exposure of personnel, or discharge to the environment. This includes research and development facilities, and the sites of API manufacturing and storage and of finished product manufacturing.
- 1.4 Where possible products should be manufactured in closed systems.

2. General

- 2.1 Facilities should be designed and operated in accordance with the main GMP principles, as follows:
 - to ensure quality of product;
 - to protect the operators from possible harmful effects of products containing hazardous substances; and
 - to protect the environment from contamination and thereby protect the public from possible harmful effects of products containing hazardous substances.
- 2.2 The production of certain products containing hazardous substances should generally be conducted in separate, dedicated, self-contained facilities.

These *self-contained facilities* may be in the same building as another facility but should be separated by a physical barrier and have, e.g. separate entrances, staff facilities and air-handling systems. The extent of the separation from adjacent facilities and sharing of common services should be determined by risk assessment.

- 2.3 In general these manufacturing facilities should be regarded as containment facilities.
- 2.4 The effective operation of a facility may require the combination of some or all of the following aspects:
 - appropriate facility design and layout, with the emphasis on safely containing the materials being handled. Manufacturing processes using closed systems or barrier technology enhance operator and product protection;
 - manufacturing process controls including adherence to standard operating procedures (SOPs);
 - appropriately designed environmental control systems (ECS) or heating, ventilation and air-conditioning (HVAC);
 - extraction systems;
 - personal protective equipment (PPE);
 - appropriate degowning and decontamination procedures;
 - industrial hygiene (monitoring staff exposure levels);
 - medical surveillance (monitoring staff exposure levels); and
 - administrative controls.

3. Glossary

The definitions given below apply to terms used in these guidelines. They may have a different meaning in other contexts.

action limit

The action limit is reached when the acceptance criteria of a critical parameter have been exceeded. Results outside these limits will require specified action and investigation.

active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

air-handling unit (AHU)

The air-handling unit serves to condition the air and provide the required air movement within a facility.

airlock

An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods (this can be a personnel airlock (PAL) or a material airlock (MAL)).

alert limit

The alert limit is reached when the normal operating range of a critical parameter has been exceeded, indicating that corrective measures may need to be taken to prevent the action limit being reached.

barrier technology

A system designed to segregate people from the product, contain contaminants or segregate two areas, which could be a barrier isolator (BI) or a restricted access barrier system (RABS):

- A BI is a unit supplied with high-efficiency particulate air (HEPA) filtered air that provides uncompromised continuous isolation of its interior from the external environment, including surrounding clean room air and personnel.
- A RABS is a type of barrier system that reduces or eliminates interventions into the critical zone. In practice, its level of contamination control is less than that of a barrier isolator.

clean room

A room or area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

commissioning

Commissioning is the documented process of verifying that the equipment and systems are installed according to specifications, placing the equipment into active service and verifying its proper action. Commissioning takes place at the conclusion of project construction but prior to validation.

containment

A process or device to contain product, dust or contaminants in one zone, preventing it from escaping to another zone.

contamination

The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediate, during production, sampling, packaging or repackaging, storage or transport.

cross-contamination

Contamination of a starting material, intermediate product or finished product with another starting material or material during production.

design condition

Design condition relates to the specified range or accuracy of a controlled variable used by the designer as a basis for determining the performance requirements of an engineered system.

environmental control system (ECS)

Environmental control system, also referred to as heating, ventilation and air-conditioning (HVAC).

facility

The built environment within which the clean area installation and associated controlled environments operate together with their supporting infrastructure.

hazardous substance or product

A product or substance that may present a substantial risk of injury, to health or to the environment.

heating, ventilation and air-conditioning (HVAC)

Heating, ventilation and air-conditioning, also referred to as environmental control system (ECS).

high efficiency particulate air (HEPA) filter

High efficiency particulate air filter.

ISO 14644

International standard relating to the design, classification and testing of clean environments (5).

laminar airflow (LAF)

A rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (modern standards no longer refer to laminar flow, but have adopted the term unidirectional airflow).

normal operating range

The range that the manufacturer selects as the acceptable values for a parameter during normal operations. This range must be within the operating range.

occupational exposure level (OEL)

Airborne concentration of substances that will not result in adverse effects to most healthy workers, exposed for 8 hours/day, 40 hours/week.

operating range

The range of validated critical parameters within which acceptable products can be manufactured.

personal protective equipment (PPE)

The necessary garments and equipment required to protect the operator in the workplace.

pressure cascade

A process whereby air flows from one area, which is maintained at a higher pressure, to another area at a lower pressure.

qualification

The planning, carrying out and recording of tests on equipment and a system, which forms part of the validated process, to demonstrate that it will perform as intended.

standard operating procedure (SOP)

An authorized written procedure, giving instructions for performing operations, not necessarily specific to a given product or material, but of a more general nature (e.g. operation of equipment, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

unidirectional airflow (UDAF)

A rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines.

validation

The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

4. Risk assessment

- 4.1 Not all products containing hazardous substances are equally potent and risk assessments should be carried out to determine the potential hazards to operators and to the environment. The risk assessment should also determine which phases of the product production and control cycles, from manufacture of the API to distribution of the finished product, would fall under the requirements of these guidelines. Risk assessments applicable to the environment should include airborne contamination as well as liquid effluent contamination.
- 4.2 Assuming that the risk assessment determines that the products or materials being handled pose a risk to the operators and/or the public and/or the environment, the

guidelines to be followed for the design and operation of the facility should be as detailed in this document.

- 4.3 The toxicological data available, such as permissible occupational exposure levels (OEL) for the product, should be taken into account when conducting the risk assessment.
- 4.4 The risk assessment should take into account the national or international occupational health and safety requirements for OELs in the work environment.

5. Product protection

- 5.1 The requirement for producing quality products, with respect to protection from contamination and cross-contamination, clean room class of air, temperature and humidity should be as for other pharmaceutical products. These requirements are covered in other WHO GMP guidelines.

6. Personal protection equipment and breathing air systems

- 6.1 The fundamental design principle for a facility and its production equipment is to provide product containment and operator protection. Should the facility and equipment design not provide adequate product containment, operator protection should be provided. If facility and equipment design are adequate, a spillage or non-routine incident could cause a hazardous situation, in which case PPE should be available. Unless otherwise specified in the material safety data sheet, operators should be protected from exposure with an appropriate method, such as by wearing:
 - flash-spun, high-density polyethylene fibre material suits or impervious washable protective suits. Integral hoods may be required depending on the respirator type used;
 - flash-spun, high-density polyethylene fibre material shoes, lower leg covers or cleanable boots;
 - suitable single-use, disposable gloves. Double gloves should be worn where direct active contact with the product cannot be avoided. Gloves should be taped or sealed on to the protective suit sleeves; and
 - respirator eye and face protection with associated breathing air systems.

- 6.2 Where breathing air systems are used, these should be provided to supply safe breathing air to the operators to prevent them from inhaling air from within the

facility. Personnel should be appropriately trained and assessed in the use of these systems before they can enter the area. The breathing air systems should comprise a protective face mask, which should form an integral part of a protective suit. The breathing air systems could be any of the systems described below:

- a central air supply system which connects to the operator's face mask by means of flexible hoses and quick coupling sockets, also called an airline respirator (AR). The air connection should incorporate a one-way air system to prevent contaminated air entering the face mask during connection or disconnection. The air supply should be treated to ensure a temperature and level of humidity that are comfortable for the operator. The air source could be a high pressure fan or an air compressor. If an air compressor is used, it should be of the oil-free type or have suitable oil removal filters fitted;
- a self-contained breathing apparatus (SCBA) or powered air purifying respirator (PAPR) that is securely attached to the operator's belt and connects to the operator's face mask. This system draws air from the room in which the operator is working and the air supply is delivered to the face mask by means of a battery-driven fan. The AR provides superior protection to the PAPR apparatus;
- for zones with lower contamination levels, a half-mask high efficiency particulate air filter (HEPA) cartridge respirator or N95-type paper filter mask may be acceptable.

- 6.3 The selection of the respirator type is based on the relationship between the accepted OEL and the respirator-certified protection factor (PF).
- 6.4 The air supplies should be filtered through a final filter, which should be a HEPA filter rated as an H13 filter according to EN 1822 (European Norm). The supply of breathing air into the face mask and/or protective suit should result in the interior of the mask and suit being at a positive pressure relative to the facility environment.
- 6.5 Central breathing air supply systems should have a 100% back-up system in the event of the main system failing. This could be in the form of a gas bottle system with at least 5 minutes supply. Changeover from the normal supply to the back-up supply should be automatic. The system should have a monitoring system and send alarm signals to a permanently manned location in the following situations:
 - failure of main air supply;
 - temperature out of specification (OOS);
 - humidity OOS;
 - carbon dioxide (CO₂) OOS;

- carbon monoxide (CO) OOS; and
 - sulfur dioxide (SO₂) OOS.
- 6.6 Breathing air should be filtered by means of pre-filters, coalescing filters and final filters to have the minimum air quality specifications of ISO 8573-1 3-9-1 and EN 12021:1999.
- 6.7 Where air is delivered through a central system the piping should not cause any contamination to be liberated into the air stream. Stainless steel piping is preferred. The final filters should be as close as possible to the operator connection points. The operator hose connection to the air supply should be a dedicated connection specific to the breathing air system (to avoid inadvertent connection to a different gas system).

7. Environmental protection

- 7.1 Due to the hazardous nature of the products being handled in the facility, neither the product nor its residues should be allowed to escape into the atmosphere or to be discharged directly to normal drainage systems.
- 7.2 The external atmosphere and the public in the vicinity of the facility should be protected from possible harm from hazardous substances.
- 7.3 If liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain.
- 7.4 Exhaust air filtration to ensure environmental protection is discussed in section 11.

8. Facility layout

- 8.1 The premises should be designed and constructed to prevent the ingress or egress of contaminants. In drawing up the facility design, attention should be paid to the level of containment provided by the equipment.
- 8.2 The link between the interior and exterior of the premises should be through airlocks (PAL and/or MAL), changing rooms, pass boxes, pass-through hatches, decontamination devices, etc. These entry and exit doors for materials and personnel should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time.
- 8.3 The changing rooms should have an arrangement with a step-over-bench. The facilities on the exit side should incorporate showers for the operators.

- 8.4 The premises should be laid out and designed so as to facilitate the required pressure cascades and containment.
- 8.5 The premises (and equipment) should be appropriately designed and installed to facilitate cleaning and decontamination.
- 8.6 The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) to ensure that the designation and conditions of use of all the rooms are correctly shown.
- 8.7 The flow of people and products should be clearly marked on the layouts and plans.
- 8.8 The activities carried out in the vicinity of the site should be indicated.
- 8.9 Plans should describe the ventilation systems, indicating inlets and outlets, in relation to other facility air inlet and outlet points.
- 8.10 The facility should be a well-sealed structure with no air leakage through ceilings, cracks or service areas.
- 8.11 Areas of the facility where exposed product presents a risk should be maintained at a negative air pressure relative to the environment.

9. Air-handling systems

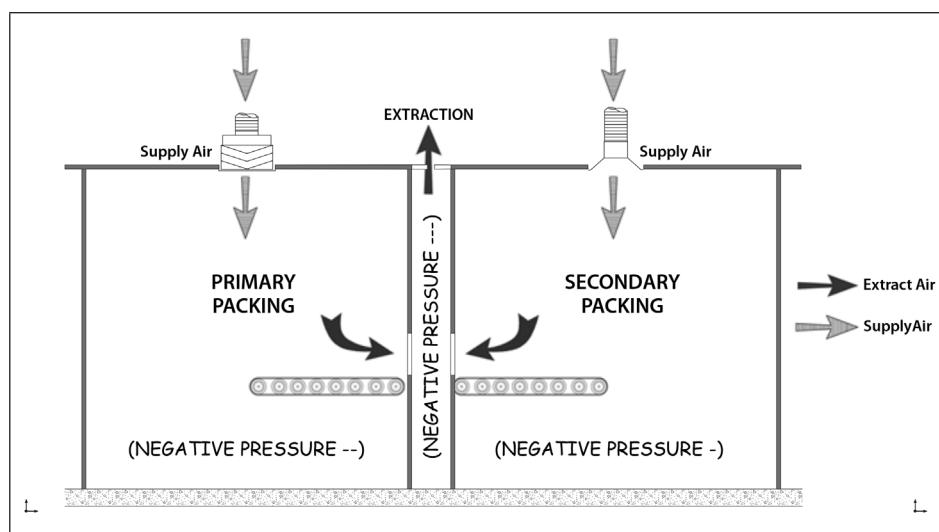
- 9.1 The HVAC system should be appropriately designed, installed and maintained to ensure protection of product, personnel and the environment.
- 9.2 The principles of airflow direction, air filtration standards, temperature, humidity and related parameters should comply with the minimum requirements as set out in Annex 2 of the fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, 2006 (2).
- 9.3 Facilities and premises dealing with hazardous substances should have the following basic air-handling characteristics:
 - There should be no direct venting of air to the outside.
 - Air-conditioning or ventilation should result in a negative pressure relative to the outside. Air pressure differentials should be such that there is no uncontrolled flow of air between the work area and the external environment.
 - Appropriate air pressure alarm systems should be provided to warn of any pressure cascade reversal or loss of design pressure status. The appropriate design, alert and action limits should be in place. System redundancies should be in place to respond appropriately to pressure cascade failure.

- The starting and stopping of the supply and exhaust air fan should be synchronized such that the premises remain at a negative pressure during start-up and shut-down.
 - The air pressure cascade within the facility, although negative relative to the environment, should comply with normal pharmaceutical pressure cascade requirements with regards to product protection, dust containment and personnel protection.
 - Visual indication of the status of room pressures should be provided in each room.
 - Air should be exhausted to the outside through HEPA filters and not be recirculated except to the same area, and provided that a further HEPA filtration stage is applied to the return air. Where HEPA filters are mentioned in these guidelines, this refers to HEPA filters with a minimum rating of H13 according to EN 1822.
 - Where possible, single-pass air-handling systems with no recirculation should be provided.
 - Exhaust air or return air should be filtered through a safe-change or bag-in-bag-out filter housing. The filter housing should contain pre-filters and HEPA filters, both of which should be removable with the safe bagging system.
 - Changing rooms should be supplied with air filtered to the same standard as that for the work area they serve.
 - Airlocks, pass-through hatches, etc., should have supply and extract air to provide the necessary air pressure cascade and containment. The final, or containment perimeter, airlock or pass-through hatch bordering on an external or non-GMP area should be at a positive pressure relative to the environment, to prevent the ingress of contaminants to the facility.
 - If the facility provides insufficient containment, and operators' garments are contaminated with dust, the operators leaving the containment area should pass through a decontamination system, e.g. air showers or a mist shower system, to assist with removing or controlling dust particles on their garments. Operators should follow this route before de-gowning to use the ablutions or canteen facilities. All garments leaving the facility for laundering should be safely bagged. Appropriate means for protecting laundry staff and prevention of contamination of other garments from non-hazardous facilities should be in place.
- 9.4 If required, appropriate measures should be taken to prevent airflow from the primary packing area (through the conveyor “mouse hole”) to the secondary packing area.

Note: This could be overcome by having a pass-through chamber over the “mouse hole”, which is maintained at a negative pressure to both primary and secondary packing. This typical arrangement is illustrated in Figure 1. This principle can be applied to other situations where containment from two sides is required.

- 9.5 Where possible, HEPA filters in the supply air system should be terminally mounted to provide protection against back-flow cross-contamination in the event of a failure in the supply airflow.
- 9.6 In some cases consideration can be given to the use of biosafety cabinets, isolation systems or glove boxes as a means for containment and operator protection.
- 9.7 There should be a system description including schematic drawings detailing the filters and their specifications, the number of air changes per hour, pressure gradients, clean room classes and related specifications. These should be available for inspection.
- 9.8 There should be an indication of pressure gradients that are monitored by means of digital or analogue pressure indicators.
- 9.9 Consideration should be given to providing an emergency power supply, e.g. diesel generators, to ensure that safe operation of the premises and systems can be maintained at all times.

Figure 1
Typical airflow pattern for contaminant



10. Air-handling units

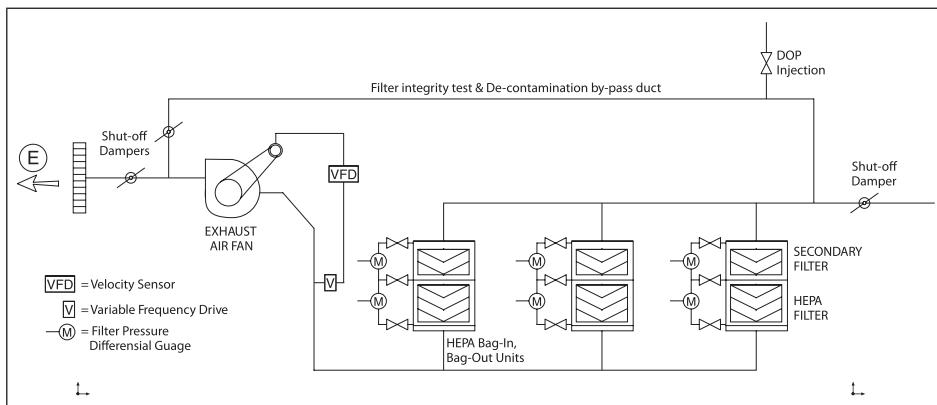
- 10.1 The air-handling units (AHUs) supplying air to the facility should conform to AHU requirements as detailed in *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials* (1) and *Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* (2) and the filtration should be consistent with the zone concepts and product protection required.
- 10.2 The decision to use return air or recirculated air should be made on the basis of a risk assessment.
- 10.3 Where a full fresh-air or single-pass system is used, an energy recovery wheel could be considered. In such cases, there should not be any potential for air leakage between the supply air and exhaust air as it passes through the wheel. The relative pressures between supply and exhaust air systems should be such that the exhaust-air system operates at a lower pressure than the supply system. (Alternatives to the energy recovery wheel, such as crossover plate heat exchangers, heat pipes and water coil heat exchangers, may be used.)
- 10.4 Risk management principles should be applied to address the potential of cross-contamination where energy wheels are used.
- 10.5 If return air is to be recirculated it should pass through a safe change filtration system before being introduced back into the supply AHU. The return air fan could form part of the AHU; however, the safe change filter should be a dedicated unit. With this arrangement the return air passes through two sets of HEPA filters in series, i.e. the return air filters in the safe change housing and the supply air HEPA filters. The supply air HEPA filters could either be located in the AHU or terminally located at the supply diffusers, depending on the clean room classification of the facility.
- 10.6 The starting and stopping of the supply and exhaust air fans, and associated system ventilation fans, should be synchronized such that the premises retain their design pressure and flow relationships during start-up and shut-down. Processing should stop when the fans are not running. This fan interlock sequence should also apply if any fan should fail, to ensure that there is no airflow reversal in the system.

11. Safe change filter housings

- 11.1 Safe change or bag-in-bag-out filter housings should be suitably designed to provide operator protection and to prevent dust from the filters entering the atmosphere when filters are changed.

- 11.2 The final filters on the safe change unit should be HEPA filters with at least an H13 classification according to EN 1822 filter standards. For dusty return, air pre-filtration may also be required to prolong the life of the HEPA filters. The pre-filtration filters should also be removable through the bag-in-bag-out method.
- 11.3 For exhaust systems where the discharge contaminant is considered particularly hazardous, two banks of HEPA filters in series should be considered to provide additional protection should the first filter fail.
- 11.4 All filter banks should be provided with pressure differential indication gauges to indicate the filter dust loading and remaining lifespan of the filters. Connection to these gauges should be copper or stainless steel and not plastic tubing, which could perish causing a contamination hazard. The tube connections on the filter casing should be provided with stopcocks, for safe removal or calibration of gauges.
- 11.5 Monitoring of filters should be done at regular intervals to prevent excessive filter loading that could force dust particles through the filter media, or could cause the filters to burst, resulting in ambient contamination.
- 11.6 Computer-based data monitoring systems may be installed to monitor filter condition.
- 11.7 Filter pressure gauges should be marked with the clean filter resistance and the change-out filter resistance.
- 11.8 Installed filter leakage tests should be performed in accordance with ISO 14644-3. Injection ports (upstream) and access ports (downstream) should, therefore, be provided for this purpose.
- 11.9 The exhaust air fan on a safe change filter system should be located after the filters so that the filter housing is maintained at a negative pressure. This poses a difficulty when carrying out filter integrity tests, and for this reason a bypass damper system should be provided, as illustrated in Figure 2, so that air can be circulated through the HEPA filters, while the scanning ports are open. Alternatively an independent booster fan system can be used, with appropriate shut-off dampers.
- 11.10 The bypass arrangement as shown in Figure 2 also permits decontamination of the filters by means of circulation of a sanitizing agent.
- 11.11 All exhaust systems from the facility, including dust extraction systems, vacuum system exhaust, fluid bed drier exhaust and coating pan exhaust, should be passed through safe change filter housings before being exhausted to the atmosphere.

Figure 2
Safe change filter bypass arrangement



- 11.12 All exhaust points outside the building should be located as far as possible from air entry points, and exit points should be at a high level to minimize the possibility of re-entrainment of exhaust air. Dominant and seasonal wind directions should be taken into account when positioning exhaust and supply points.
- 11.13 Where excessively dust-laden air is handled, a dust collector or bag house should be considered, with the dust collector being located in an enclosed room maintained at a negative pressure. Access control, maintenance staff, personal protection equipment (PPE) and breathing air systems should then be provided to protect the operators during removal of dust from the collector bins.
- 11.14 Portable vacuum cleaners and portable dust collectors should be fitted with H13 HEPA filters. These types of units should be emptied and cleaned in a room which is under negative pressure relative to the environment. Personnel should be provided with suitable PPE.
- 11.15 Records of the safe disposal of all contaminated filters and dust should be kept.

12. Personnel decontamination systems

- 12.1 If required, a means of preventing contaminants from leaving the facility on the garments of personnel should be provided. This could be in the form of an air shower; mist shower, water shower or appropriate device.
- 12.2 An air shower comprises an airlock where high velocity air is supplied through air nozzles (e.g. from the sides of the airlock) in order to dislodge dust particles. Air

extraction grilles (e.g. at low level) should draw the air away and return it to the filtration system. Some air showers may also incorporate a vertical unidirectional airflow section at the exit end, to flush contaminants away.

Note: When air showers are used these should be correctly designed to effectively extract dust.

Air filtration of the supply air and return or exhaust air should comply with the same filtration standards as used in the manufacturing facility. Normally the fan should be activated by opening the door as the operator enters the shower, with a timing device on the exit door interlock to allow sufficient time for the decontamination process to be effective.

- 12.3 Flushing devices similar to air or mist showers for personnel could be used at material exits to assist with removing contaminants.
- 12.4 Wet mist or fog decontamination systems for operators can be employed for deactivating contaminants on the operator's garments, or causing contaminants to adhere to the garments so that they are not easily liberated.
- 12.5 Personnel should change into clean garments after having taken a shower.

13. Effluent treatment

- 13.1 Liquid and solid waste effluent should be handled in such a manner as not to present a risk of contamination to the product, personnel or to the environment.
- 13.2 All effluent should be disposed of in a safe manner, and the means of disposal should be documented. Where external contractors are used for effluent disposal they should have certification authorizing them to handle and treat hazardous products.

14. Maintenance

- 14.1 The efficient and safe operation of a facility handling hazardous materials is reliant on regular maintenance being carried out, to ensure that all parameters remain within specified tolerances. See *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials* (1) or WHO Technical Report Series, No. 937, Annex 2, section 8.3 (2) for further details on maintenance.

15. Qualification and validation

- 15.1 System qualification and validation should be carried out as described in other WHO guidelines.

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3.8 WHO good manufacturing practices for investigational products

Annex 7, WHO Technical Report Series, 1044, 2022 (revised)

Background

In view of an old publication date, and the recent need for new guidelines arising from inspections carried out for COVID-19 therapeutics, the World Health Organization (WHO) Prequalification Team – Inspection Services (PQT/INS) raised the urgency for a revision of the WHO *Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans* (1). The fifty-fifth Expert Committee on Specifications for Pharmaceutical Preparations concurred with this proposal.

The objective of this update is to bring the guideline in line with current expectations and trends in good practices and to harmonize the text with the principles of other related international guidelines.

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1. Introduction

- 1.1 Investigational products are used for testing purposes; as a reference in clinical trials and field trials; as a placebo; for an unauthorized indication; or to gain further information about the authorized form.
- 1.2 In some cases, marketed products that have been repackaged or modified in some way are used for investigational purposes.
- 1.3 The legal status of investigational products varies from country to country.
- 1.4 These products are sometimes not covered by legal and regulatory provisions in the areas of good practices and inspection. In such circumstances, risks related to investigational products are increased by lack of adherence to good manufacturing practices (GMP), risk of contamination and cross-contamination, and shortcomings in clinical trial designs, blinding and randomization. In addition, there are instances where there is incomplete knowledge of the potency and safety of the investigational product.
- 1.5 There are further risks associated with the production, validation, testing, control, shipping, storage and use of investigational products.
- 1.6 To minimize risk, to ensure the safety of the subjects participating in clinical trials, and to ensure that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture, investigational products should be manufactured, packaged, tested, handled, stored and distributed in accordance with an effective quality management system, applicable good practice guidelines and the recommendations contained in this guideline.
- 1.7 Other guidelines and good practices should be taken into account, where relevant, and as appropriate to the stages of development, production and control of the product.
- 1.8 The quality management system should include provision for changes to be made whenever necessary as knowledge of the process increases over time, and in accordance with the stage of development of the product.
- 1.9 Investigational products should be manufactured in a manner:
 - that is compliant with GMP, as appropriate to the stage of development;
 - that ensures that subjects of clinical trials will be protected from poor-quality products resulting from unsatisfactory manufacturing;
 - that ensures consistency between and within batches of the investigational product;

- that enables a review of the data derived from the investigational products used against the future commercial product.
- 1.10 The selection of an appropriate dosage form for clinical trials is important. While it is accepted that the dosage form used in early trials may be very different from the anticipated final formulation (for example, a capsule instead of a tablet), in the pivotal phase III studies, it should be similar to the projected commercial presentation; otherwise these trials will not necessarily prove that the marketed product is both efficacious and safe. If there are differences between the clinical trial dosage form and commercial dosage forms, scientific justification and data should be submitted to the registration authorities to demonstrate that the final dosage form is equivalent, in terms of bioavailability and stability, to that used in the clinical trials.
- 1.11 The quality control of investigational products should be appropriate to the stage of development. For example, dosage forms in phase III clinical studies should be characterized and assured at a similar level as for commercially manufactured products.
- 1.12 Where production or quality control is transferred from one site to another, the recommendations in the guideline for transfer of technology should be considered (2).
- 1.13 This document should be read in conjunction with other WHO good practice guidelines (3–11).

2. Scope

- 2.1 The recommendations in this guideline are applicable to investigational products for human use.

3. Glossary

The definitions given below apply to the terms used in this guideline. They have been aligned as much as possible with the terminology in related WHO guidelines and good practices and included in the WHO *Quality Assurance of Medicines Terminology Database: list of terms and related guideline*,¹ but may have different meanings in other contexts.

¹ https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/mqa-terminology-sept-2020.pdf?sfvrsn=48461fc_5.

clinical trial. Any systematic study on pharmaceutical products in human subjects, whether in patients or other volunteers, in order to discover or verify the effects of, or identify any adverse reaction to, investigational products; and to study the absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety.

Clinical trials are generally divided into phases I–IV. It is not possible to draw clear distinctions between these phases, and different opinions about details and methodology exist. However, the individual phases, based on their purposes as related to the clinical development of pharmaceutical products, can be briefly defined as follows:

- **Phase I.** These are the first trials of a new active ingredient or new formulation in humans, often carried out in healthy volunteers. Their purpose is to make a preliminary evaluation of safety, and an initial pharmacokinetic and pharmacodynamic profile of the active ingredient.
- **Phase II.** The purpose of these therapeutic pilot studies is to determine activity and to assess the short-term safety of the active ingredient in patients suffering from a disease or condition for which it is intended. The trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (for example, placebo-controlled) design. This phase is also concerned with the determination of appropriate dose ranges and regimens and (if possible) the clarification of dose–response relationships in order to provide an optimal background for the design of extensive therapeutic trials.
- **Phase III.** This phase involves trials in large (and possibly varied) patient groups for the purpose of determining the short- and long-term safety and efficacy balance of formulations of the active ingredient, and assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (for example, clinically relevant drug interactions and factors leading to differences in effect, such as age). The trials should preferably be randomized double-blind trials, but other designs may be acceptable, such as long-term safety studies. In general, the conditions under which the trials are conducted should be as close as possible to the normal conditions of use.
- **Phase IV.** In this phase, studies are performed after the pharmaceutical product has been marketed. They are based on the product characteristics on which the marketing authorization was granted and normally take the form of post-marketing surveillance and assessment of therapeutic value or treatment strategies. Although methods may differ, the same scientific and ethical standards should apply to phase IV studies as are applied in pre-marketing studies. After a product has been placed on the

market, clinical trials designed to explore new indications, new methods of administration or new combinations are normally regarded as trials of new pharmaceutical products.

expiry date. The date placed on the container or label of an investigational product designating the time during which the investigational product is expected to remain within established shelf-life specifications if stored under defined conditions, and after which it should not be used.

investigational product. Any pharmaceutical product, including a new product, existing product for a new indication, reference product or placebo, being tested or used as a reference in a clinical trial.

investigator. The person responsible for the trial and for protecting the rights, health and welfare of the subjects in the trial. The investigator must be an appropriately qualified person, legally allowed to practice medicine or dentistry.

monitor. A person appointed by the sponsor who is responsible for monitoring and reporting the progress of the trial and for the verification of data.

order. An instruction to process, package and ship a certain number of units of an investigational product.

pharmaceutical product. For the purpose of this document, this term is defined in the same way as in the *WHO handbook for good clinical research practices* (4), that is, as any substance or combination of substances that has a therapeutic, prophylactic or diagnostic purpose, or is intended to modify physiological functions, and is presented in a dosage form suitable for administration to humans.

product specification file. The product specification file brings together and contains or refers to all of the essential reference documents to ensure that investigational products are manufactured according to good manufacturing practice for investigational products and the clinical trial authorization. It should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions.

protocol. A document that gives the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator or institution involved and the sponsor, and can, in addition, function as a contract.

reference sample. A sample of a batch of starting material, packaging material, product contained in its primary packaging, or finished product that is stored for the purpose of being analysed, should the need arise. This may include storage in a suitable bulk container.

retention sample. A sample of a packaged unit from a batch of finished product for each packaging run or trial period. It is stored for identification purposes – for example, presentation, packaging, labelling, leaflet, batch number and expiry date – should the need arise.

shipping/dispatch. The packing for shipment and sending of ordered products for clinical trials.

sponsor. An individual, company, institution or organization that takes responsibility for the initiation, management and financing of a clinical trial. When an investigator independently initiates and takes full responsibility for a trial, the investigator also then assumes the role of the sponsor.

4. Quality management

- 4.1 There should be a comprehensively designed, clearly defined, documented and correctly implemented quality management system in place. Senior management should assume responsibility for this, as well as for the quality of the investigational product.
- 4.2 All parts of the quality system should be adequately resourced and maintained.
- 4.3 The quality system should incorporate the principles of GMP, which should be applied appropriately to each stage of the development, including technology transfer and the interface between the manufacture and the trial sites (for example, with regard to shipment, storage and labelling).
- 4.4 The quality management system should ensure that:
 - products are designed and developed in accordance with the requirements of this document and other associated guidelines, such as good laboratory practices (3), good clinical practices (4), GMP (5, 6) and good storage and distribution practices (7), where appropriate;
 - responsibilities are clearly defined in job descriptions;
 - operations are clearly described in a written form;
 - arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
 - all necessary controls on starting materials, intermediate products, bulk products and other in-process controls should be in place;
 - maintenance, calibration, qualification and validation are carried out where necessary;

- the finished product is correctly processed and checked according to the defined procedures;
- changes are appropriately managed and documented, and records are maintained;
- deviations are investigated and recorded with an appropriate level of root cause analysis done and appropriate corrective and preventive actions identified and taken;
- investigational products are stored, distributed and subsequently handled in accordance with relevant good practice guidelines.

5. Quality risk management

- 5.1 There should be a system for quality risk management (8).
- 5.2 The system for quality risk management should cover a systematic process for the assessment, control, communication and review of risks to the quality of the product and, ultimately, to the protection of the trial subjects and patients.
- 5.3 The quality risk management system should ensure that:
 - the evaluation of the risk is based on scientific knowledge and experience with the process and product;
 - procedures and records for quality risk management are retained;
 - the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.
- 5.4 Quality risk management should be applied both prospectively and retrospectively, as appropriate.

6. Personnel

- 6.1 There should be a sufficient number of appropriately qualified personnel available to carry out all the tasks for which the manufacturer of investigational products is responsible.
- 6.2 Individual responsibilities should be clearly defined, recorded as written descriptions and understood by the persons concerned.
- 6.3 A designated person, with a broad knowledge of product development and clinical trial processes, should ensure that there are systems in place that meet the requirements of this guideline and other relevant good practice guidelines.

- 6.4 Personnel involved in the development, production and control of investigational products should have appropriate qualifications. They should be trained in relevant good practices and the requirements specific to investigational products. All personnel, prior to and during employment, as appropriate, should undergo health examinations. Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials or products until the condition is no longer judged to be a risk. Records should be maintained. No cosmetics or jewellery should be worn.
- 6.5 Persons responsible for production and quality should be clearly identified and independent from one another, where applicable.
- 6.6 A person should be designated to be responsible for the release of batches.
- 6.7 Appropriate protective garments should be worn, based on operations and risk.
- 6.8 Smoking, eating, drinking, chewing and keeping plants, food, drink, smoking material and personal medicines should not be permitted in any area where they might adversely influence product quality.
- 6.9 Visitors and untrained persons should normally not be allowed into production and quality control areas. When entry is required, it should then be under instruction and close supervision.

7. Documentation

- 7.1 Good documentation is an essential part of a quality management system. Documents should be appropriately designed, prepared, reviewed and distributed. They should also be appropriate for their intended use (12).
- 7.2 Documents should be approved, signed and dated by the appropriate responsible persons. No authorized document should be changed without prior authorization and approval.

7.1 Specifications

- 7.3 Specifications with limits for impurities and degradation products, where applicable, should be available (for example, for raw materials, starting materials, placebos, and intermediate, bulk and finished products). There should be specifications for packaging materials.
- 7.4 In developing specifications, attention should be paid to the characteristics that affect the efficacy and safety of products, such as:

- the sterility, potency, assay and other quality attributes of the product (content uniformity can be used for quantitation of drug product assay or unitary dose, where appropriate);
 - the release of active ingredients from the dosage form (for example, dissolution profile);
 - the suitability of the package size for the requirements of the trial, where applicable;
 - the stability of the product, including expected stability where data have been obtained from accelerated conditions, if needed;
 - the preliminary storage conditions;
 - the shelf-life of the product.
- 7.5 As a result of new experience in the development of an investigational product, specifications may be changed by following a documented procedure. Changes should be authorized by a responsible person. Each new version should take into account the latest data and information, current technology, and regulatory and pharmacopoeial requirements. There should be traceability of the previous version or versions. The reasons for changes should be recorded. The impact of the change on any ongoing clinical trials, product quality, stability, bioavailability and bioequivalence (where applicable) should be considered, based on risk.

7.2 Order

- 7.6 An order should be available for the request of a certain number of units for processing, packaging, storage and shipping.
- 7.7 The order should be given by or on behalf of the sponsor to the manufacturer of an investigational product.
- 7.8 The order should be in writing (for example, by paper or electronic means, or a combination thereof), be authorized and contain sufficient detail, including reference to the approved product specification file (see below) and the relevant clinical trial protocol, as appropriate.
- 7.9 Where commercially available products are obtained to be used as reference products (for example, for use in bioequivalence studies), the relevant documentation, such as a purchase order, an invoice, and storage and transport records, should be maintained and available for inspection.

7.3 Product specification file

- 7.10 A product specification file (or files) should contain, or refer to, files containing all the information necessary to prepare detailed written instructions on

processing, packaging, quality control testing, batch release, storage conditions and shipping.

7.11 The information should form the basis for assessment of the suitability for certification and release of a particular batch by the designated responsible person. It should include, or refer to, the following documents (13):

- specifications and analytical methods for starting materials, packaging materials, intermediate product, bulk product and finished product;
- manufacturing methods;
- in-process testing and methods;
- approved label copy;
- relevant clinical trial authorizations and amendments thereof, clinical trial protocol and randomization codes, as appropriate;
- relevant technical agreements with contract givers and acceptors, as appropriate;
- stability plan and reports;
- storage and distribution conditions;
- details of the supply chain, including manufacturing, packaging, labelling and testing sites for the investigational products, preferably in the format of a comprehensive diagram.

Note: The contents will vary depending on the product and stage of development. Where different manufacturing steps are carried out at different locations, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations.

7.4 Manufacturing formulae and processing instructions

7.12 Every manufacturing operation or supply should have clear written instructions for personnel, based on the relevant product specification file and trial details, and written records to enable the details of activities to be reconstructed.

7.13 As a result of new experience in the development of an investigational product, manufacturing formulae and processing instructions may be changed by following a documented procedure. Each new version should take into account the latest data and information, current technology, and regulatory and other requirements. There should be traceability to previous versions. The reasons for changes should be recorded. The impact of the change on any ongoing clinical trial, product quality, stability, bioavailability and bioequivalence (where applicable) should be considered, based on risk. Changes should be authorized by a responsible person.

- 7.14 Batch processing and packaging records, as well as product specification files, should be retained for a defined period of time.
- 7.15 Where the data are intended for inclusion in an application for product registration (marketing authorization) purposes, the records should be maintained for 30 years from authorization or until the end of the life cycle of the product, whichever is shorter.

7.5 Packaging instructions

- 7.16 The theoretical number of units to be packaged should be specified before the start of the packaging operation. This should include the number of units necessary for carrying out quality controls and the number of samples from each batch used in the clinical trial to be kept as retention samples. Reconciliation of units packed and primary labels should be carried out at defined intervals, where required, and at the end of the packaging and labelling process.
- 7.17 Investigational products should normally be packed individually for each subject included in the clinical trial.

7.6 Labelling instructions

- 7.18 Labelling should be performed by a site authorized by the sponsor, under the supervision of an appropriately qualified individual (for example, a health care professional or clinical trial monitor) and checked by a second person, in accordance with GMP principles and standard operating procedures. This additional labelling should be recorded in both the trial documentation and in the batch records.
- 7.19 Investigational products should be labelled in accordance with relevant legislation or best practices. Examples of information that the label should include are as follows:
- the name, address and telephone number of the sponsor, contract research organization or investigator;
 - the statement “For clinical research use only”, or similar wording;
 - a reference number indicative of the trial, site, investigator and sponsor, if not given elsewhere;
 - a batch or code number;
 - the trial subject, patient identification number and a treatment code;
 - a reference to the directions or instructions for use;
 - information on storage conditions;
 - an expiry date, use-by date or retest date (month and year) or similar, where appropriate;

- a dosage form and route of administration;
 - whether for single or multiple use, where applicable;
 - the quantity of dosage units and, in the case of open trials, the name or identifier and the strength or potency.
- 7.20 Additional information may be displayed in accordance with the order (such as treatment period, standard warnings).
- 7.21 When necessary for blinding purposes, the batch number may be provided separately (see also section 11.3 below).
- 7.22 A copy or electronic record of each type of label should be kept in the batch packaging record.
- 7.23 The address and telephone number of the main contact for information on the product or clinical trial, and for emergency unblinding, need not appear on the label where the subject has been given a leaflet or card that provides those details and has been instructed to keep that information in their possession at all times.
- 7.24 Particulars should appear in the official language or languages of the country in which the investigational product is to be used. This may be provided electronically.
- 7.25 Where all the required information cannot be displayed on primary packaging, secondary packaging should be provided bearing a label with those particulars. The primary packaging should nevertheless contain information such as the name of sponsor, contract research organization or investigator; route of administration; batch or code number; trial reference code; and the trial subject identification number or treatment code. Where required, for example in open label trials, the product name and strength of the product should be displayed.
- 7.26 Symbols or pictograms may also be used or included to clarify certain information. Warnings and handling instructions may be displayed.
- 7.27 If it becomes necessary to change the use-by date, an additional label should be affixed to the investigational product. This additional label should state the new use by date and repeat the batch number. The original batch number should remain visible. This labelling activity should be performed in accordance with GMP principles and standard operating procedures and should be checked by a second person. This additional labelling should be recorded both in the trial documentation and in the batch records.

7.7 Batch manufacturing, packaging and testing records

- 7.28 Processing, packaging and testing records should be kept in sufficient detail for the sequence of operations to be accurately traced.

7.8 Coding (or randomization) systems

- 7.29 Procedures should be established for the generation, security, distribution, handling and retention of any randomization code used in packaging investigational products and code-break mechanisms. The appropriate records should be maintained.
- 7.30 The coding system must permit the determination of the identity of the actual treatment product received by individual subjects, without delay, in an emergency situation.

8. Premises

- 8.1 Premises where investigational products are manufactured should be located, designed, constructed and maintained to suit the operations to be carried out.
- 8.2 The layout and design of premises should aim to minimize the risk of errors and mix ups and permit effective cleaning and maintenance in order to avoid contamination, cross-contamination and, in general, any adverse effect on the quality of the products. Where possible, the use of unidirectional flows for personnel, materials, products and waste should be established and maintained.
- 8.3 Attention should be paid to line clearance in order to avoid mix-ups.
- 8.4 Validated or verified cleaning and sanitization procedures, as appropriate, should be followed in order to prevent cross-contamination. Since the characteristics and toxicity of some investigational materials may not be fully known, cleaning is of particular importance to avoid cross-contamination. The visual inspection after cleaning, sampling and test procedures should be appropriate and the acceptance limits applied should be scientifically justifiable. Cleaning and sanitizing agents should not become a source of contamination.
- 8.5 Where identified through risk assessment, campaign production should be considered. In other cases based on risk, dedicated and self-contained facilities should be considered.
- 8.6 Ingress of contaminants should be avoided and controls should be implemented to prevent contamination of the environment, as required.

9. Equipment and utilities

- 9.1 Equipment and utilities should be selected, located, constructed, qualified (as appropriate) and maintained to suit the operations to be carried out.
- 9.2 The layout, design, installation and use of equipment and utilities should aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, a build-up of dust or dirt and, in general, any adverse effect on the quality of products, and should support reproducibility and robustness of the process.
- 9.3 Computerized systems used to acquire, process and store GMP data should be validated. The extent of validation should be based on risk assessment (8).

10. Materials

10.1 Starting and packaging materials

- 10.1 The consistency of the production of investigational products may be influenced by the quality of the starting materials. Their physical, chemical and, when appropriate, microbiological properties should therefore be defined, documented in their specifications, and controlled.
- 10.2 Existing compendial standards, when available, should be used.
- 10.3 Specifications for active ingredients and excipients should be as comprehensive as possible, given the current state of knowledge.
- 10.4 Specifications for both active ingredients and excipients should be reassessed and updated when required.
- 10.5 In addition to the specifications, detailed information on the active ingredients, excipients and packaging materials should be available. This includes materials of animal origin.

10.2 Chemical and biological reference standards for analytical purposes

- 10.6 Reference standards (WHO or national standards) should be used, if available. Otherwise, the reference substances for the active ingredients should be prepared, tested and authorized for use as reference materials by the producer of the investigational product, or by the producer of the active ingredients used in the manufacture of that product (10).

10.3 Principles applicable to reference products for clinical trials

- 10.7 In a study where an investigational product is being compared to a marketed product, the integrity and quality of the reference (such as final dosage form, packaging materials or storage conditions) should be ensured.
- 10.8 If significant changes are to be made in the product, data should be available (for example, on stability and comparative dissolution) that demonstrate that those changes do not influence the original quality characteristics of the product.

11. Production

- 11.1 Products intended for use in clinical trials should be manufactured in accordance with the requirements of this guideline and, where required by national legislation, in licensed facilities. Manufacturing operations should be controlled as appropriate to the phase of development and scale of manufacture.
- 11.2 Where activities are outsourced to contract facilities and the products to be manufactured or controlled are intended for use in clinical trials, the contract must then clearly state the responsibilities of each party in compliance with this guideline and WHO GMP (5). Close cooperation between the contracting parties is essential.

11.1 Manufacturing operations

- 11.3 As process validation may not always be complete during the development phase of products, provisional quality attributes, process parameters and in-process controls should be identified, based on risk management principles and experience with the products or analogous products.
- 11.4 The necessary processing instructions should be identified and may be adapted, based on the experience gained in production.
- 11.5 Where processes such as mixing have not been validated, additional quality control testing may be necessary.
- 11.6 For sterile investigational products, the sterility assurance should be no less than for commercial products (11).

11.2 Packaging and labelling

- 11.7 The packaging and labelling of investigational products are likely to be more complex and more liable to errors (which are also harder to detect) when “blinded” labels are used than for commercial products. Supervisory procedures, such as label reconciliation, line clearance, and other controls, including independent checks by quality unit personnel, should be intensified accordingly.

- 11.8 The packaging must ensure that the investigational product remains in good condition during transport and storage, within specified limits of temperature, relative humidity and light, as appropriate. Any opening of, or tampering with, the outer packaging during transport should be readily visible.

11.3 Blinding operations

- 11.9 In the preparation of blinded products, the blind should be maintained until it is required to enable its identification.
- 11.10 A coding system should be introduced to permit the identification of blinded products, also in the case of an emergency. The code, together with the randomization list, must enable the identification of the product, including any necessary traceability to the codes and batch number of the product before the blinding operation.
- 11.11 Controls should be applied to verify the similarity in appearance and other physical characteristics, such as the odour and colour of blinded investigational products. Maintenance of blinding during the study should be ensured and verification of the effectiveness of blinding should be performed and recorded.

12. Quality unit (including quality control)

- 12.1 Quality control should cover, for example, the sampling and testing of materials and products. The analytical procedures should be suitable for their intended purpose, ensuring that materials and products are not released for use or supply until their quality has been judged to be compliant with the specifications.
- 12.2 Each batch of product should be tested in accordance with the specifications included in the product specification file and should meet its acceptance criteria.
- 12.3 Bulk product release should cover all relevant factors, including production conditions, the results of in-process testing, a review of manufacturing documentation, and compliance with the product specification file and the order. Finished product release should cover, in addition to the bulk product assessment, all relevant factors, including packaging conditions, the results of in-process testing, a review of packaging documentation and compliance with the product specification file and the order.
- 12.4 Reference and retention (control) samples of each batch of product should be retained.
- 12.5 Retention samples should be kept until the clinical report has been submitted to the regulatory authorities or at least two years after the termination or completion

of the relevant clinical trial, whichever is longest. This is in order to enable the confirmation of product identity in the event of, and as part of an investigation into, inconsistent trial results.

- 12.6 The storage location of reference and retention samples should be defined in a technical agreement between the sponsor and manufacturer and should enable timely access by the competent authorities.
- 12.7 The retained sample should be of sufficient size to perform the full analytical controls at least twice on the batch in accordance with the investigational product dossier submitted for authorization in order to conduct the clinical trial.
- 12.8 Where data and information are stored as electronic records, such systems should comply with the requirements of WHO guidelines for computerized systems (9).
- 12.9 The release of a batch of an investigational product should only occur after the designated responsible person and sponsor, as required, have certified that the product meets the relevant requirements. These requirements include the assessment of, as appropriate:
 - batch records, including control reports, in-process test reports, changes, deviations and release reports demonstrating compliance with the product specification file, the order, and randomization code;
 - production conditions;
 - the qualification status of facilities and the validation status of processes and methods, as appropriate;
 - the examination of finished packs;
 - where relevant, the results of any analyses or tests performed after importation;
 - stability reports;
 - the source and verification of conditions of storage and shipment;
 - audit reports concerning the quality system of the manufacturer, where applicable;
 - documents certifying that the manufacturer is authorized to manufacture investigational products or comparators for export by the appropriate authorities in the country of export;
 - where relevant, regulatory requirements for marketing authorization, GMP standards applicable and any official verification of GMP compliance.

Note: The relevance of the above elements is affected by the country of origin of the product, the manufacturer and the marketed status of the product.

13. Qualification and validation

- 13.1 The scope of qualification and validation required should be determined based on risk assessment.
- 13.2 For sterile products, there should be no reduction in the degree of validation of sterilizing equipment required. Validation of aseptic processes presents special problems when the batch size is small due to the low number of units filled for a validation exercise. Filling and sealing, which is often done by hand, can compromise the maintenance of sterility. Enhanced attention should be given to operator training and the qualification of their aseptic technique. Sterility testing methods should be validated.
- 13.3 Attention should also be given to environmental monitoring.

14. Complaints

- 14.1 There should be a written procedure describing the managing of complaints.
- 14.2 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated.
- 14.3 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.
- 14.4 All decisions made and measures taken as a result of a complaint should be recorded.
- 14.5 The competent authorities should be informed if a manufacturer is considering action following the identification of serious quality problems with a product that may be impacting trial subjects or patients.
- 14.6 The conclusions of the investigations carried out in response to a complaint should be discussed between the manufacturer and the sponsor (if different) or between the persons responsible for manufacture and those responsible for the relevant clinical trial in order to assess any potential impact on the trial and on the product development, and to determine the cause and take any necessary corrective action.

15. Recalls

- 15.1 There should be a written procedure describing the managing of a recall of investigational products.
- 15.2 Recall procedures should be understood by the sponsor, investigator and monitor, in addition to the person or persons responsible for recalls.

- 15.3 The recall of a product should be documented and inventory records should be kept.
- 15.4 The recall process should be tested routinely and the results of mock recall should be recorded to demonstrate effectiveness.

16. Returns

- 16.1 There should be a written procedure describing the managing of returns of investigational products. The returns should be under agreed conditions, as defined by the sponsor.
- 16.2 Returned investigational products should be clearly identified and stored in a dedicated area in a controlled manner.
- 16.3 Inventory records of returned products should be kept.

17. Shipping

- 17.1 The shipping of investigational products should be carried out in accordance with written procedures laid down in the protocol or shipping order given by the sponsor.
- 17.2 Acceptable shipping conditions, including temperature and light protection, based on product attributes, phase-appropriate stability data and risk assessment, should be observed. If required, a calibrated temperature monitor should be kept adjacent to the product, and the product shipment should be packaged appropriately to ensure that it will reach its destination intact and maintain the appropriate temperature profile during that time.
- 17.3 A shipment is sent to an investigator after following the defined release procedures, for example, quality control, certification and authorization by the sponsor and responsible person, as appropriate. Releases should be recorded.
- 17.4 The sponsor should ensure that the shipment will be received and acknowledged by the correct addressee, as stated in the protocol.
- 17.5 A detailed inventory of the shipments made by the manufacturer should be maintained and should make particular mention of the addressee's identification.
- 17.6 The transfer of investigational products from one trial site to another should be done in exceptional cases only. Such transfers should be justifiable, documented and carried out in accordance with a written procedure. Repackaging or relabelling should normally be done by the manufacturer or by authorized personnel at a hospital, health centre or clinic that meets the requirements. Records should be maintained and provide full traceability of the product, batch and activities.

18. Destruction

- 18.1 The sponsor is responsible for the destruction of unused, partially used or returned investigational products. These should normally not be destroyed by the manufacturer without prior authorization by the sponsor.
- 18.2 Destruction operations should be carried out in accordance with written procedures and environmental safety requirements.
- 18.3 The delivered, used and recovered quantities of a product should be recorded, reconciled and verified by or on behalf of the sponsor for each trial site and each trial period. The destruction should be carried out only after any discrepancies have been investigated and satisfactorily explained, and the reconciliation has been accepted.
- 18.4 Destruction operations should be recorded in such a manner that all operations are accounted for. These records should be kept by the sponsor.
- 18.5 A certificate of destruction should be available containing the necessary detail to enable traceability of the product, batch and related information.

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3.9 IAEA - WHO guideline on good manufacturing practices for investigational radiopharmaceutical products

Annex 3, WHO Technical Report Series, 1044, 2022 (new)

Background

In view of the rapidly expanding field of molecular imaging and targeted radiopharmaceutical therapy, combined with the absence of dedicated guidance specific to the manufacture of investigational radiopharmaceuticals used in both early and late clinical trials, the World Health Organization (WHO), in partnership with the International Atomic Energy Agency (IAEA), has raised the urgency for the generation of a new *IAEA/WHO guideline on good manufacturing practices for investigational radiopharmaceutical products*.

The objective of this guideline is to meet current expectations and trends in good manufacturing practices specific to investigational radiopharmaceuticals used in clinical trials (that is, phase I, phase II and phase III trials) and to harmonize the text with the principles from other related international guidelines.

This text was developed in alignment with the *Good manufacturing practices; supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans* (1). A draft working document was made available online for comments (2).

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1. Introduction

- 1.1 Radiopharmaceuticals are rapidly re-emerging as clinically valuable tools used in the diagnosis and treatment of various types of disease. Molecular imaging agents offer unparalleled methodology not only to help elucidate the presence and the extent of disease but also to help characterize the disease, select specific patients for a particular therapy and evaluate a treatment response. Additionally, novel targeted radioligand therapies offer alternatives to patients for whom no other treatment options exist.
- 1.2 This rapid expansion has been accompanied by a set of challenges due to the complexity and unique nature of these agents. One of the main challenges associated with novel radiopharmaceutical development is how to define the proper balance with respect to the controls required when conducting early clinical studies of manufacture of investigational radiopharmaceuticals, and the subsequent implementation of additional controls as the radiopharmaceutical is developed further into pivotal phase III trials. Having inadequate manufacturing controls during early clinical evaluations either carries the risks of unnecessary patient harm or jeopardizes the validity of the collected study results. On the other hand, redundant manufacturing controls, particularly in the initial stages of development, carry the risk of slowing the pace of clinical development of potentially lifesaving therapies. This risk is further intensified by other factors such as the high costs and lengthy time associated with the actual clinical conduct of the study, the completion of the preclinical evaluation of the agent, and the low probability of successful marketing approval. In light of these challenges, a balanced approach with respect to manufacturing process controls is essential, as the degree of manufacturing process controls is correlated with the particular stage of radiopharmaceutical development, the nature of the agent itself, and the clinical study goals.
- 1.3 This guidance provides recommendations on the minimum standards that should be in place when preparing novel radiopharmaceuticals for phases I–III clinical investigations that do not have a marketing authorization.
- 1.4 Investigational radiopharmaceuticals are used for testing purposes, as a reference in a clinical trial for an unauthorized indication, and to gain further information about the authorized form.
- 1.5 Depending on the country, these products are sometimes not covered by legal and regulatory provisions in the areas of good manufacturing practices (GMP). The lack of both high-level GMP requirements and prior knowledge of the risk of contamination and cross-contamination of products contributes to the risk of using them in human subjects. In addition, the risk may be further increased in cases of incomplete knowledge of the potency, human biodistribution, and toxicity of the investigational radiopharmaceuticals.

- 1.6 To minimize the risks and to ensure that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory production, investigational radiopharmaceuticals should be produced and managed in accordance with an effective quality management system and the recommendations contained in this guideline.
- 1.7 Procedures should be flexible to allow for changes whenever necessary through a properly controlled and traceable change management system, as knowledge of the process increases in accordance with the stages of development of the product.
- 1.8 Investigational radiopharmaceuticals should be produced in a manner that is compliant with GMP requirements that are specific to the particular stage of agent development.
- 1.9 As the clinical development of radiopharmaceutical progresses from phases I-II to the pivotal phase III and commercial stage, additional manufacturing process controls and analytical method validation should be implemented so as to ensure:
 - that subjects of clinical trials will be protected from poor-quality products due to unsatisfactory manufacturing;
 - that consistency exists between and within batches of the investigational radiopharmaceuticals;
 - that consistency exists between the investigational product and the future commercial product.
- 1.10 The selection of an appropriate dosage form for clinical trials is important. While it is accepted that the dosage form in early trials may be different from the anticipated final formulation (for example, different strength or different buffers, radiostabilizers and other excipients), in the pivotal phase III studies it should be equivalent to the projected commercial presentation in terms of the expected biodistribution profile. If there are significant differences between the investigational and commercial dosage forms, data should be submitted to the registration authorities to demonstrate that the final dosage form is equivalent, in terms of biodistribution and stability, to that used in the clinical trials.
- 1.11 The quality of investigational radiopharmaceuticals should be appropriate for the particular stage of development. For example, it should be feasible to apply only the critical manufacturing controls for agents in phase I and phase II trials, while the manufacture of investigational radiopharmaceuticals for phase III clinical studies should generally have the same degree of applied controls as for commercial manufactured products.
- 1.12 This document should be read in conjunction with other World Health Organization (WHO) GMP guidelines, including good clinical practices, good documentation

practices and International Atomic Energy Agency (IAEA) radiation protection documents related to radiopharmaceuticals (3–9).

2. Scope

- 2.1 The recommendations in this guideline are applicable to investigational radiopharmaceutical products for human use.
- 2.2 The recommendations of this guideline do not apply to radiopharmaceuticals in phase IV (with marketing authorization) that already have regulatory authority approval for a certain indication but might be used to conduct a clinical study for a different indication. In those situations, the IAEA/WHO guideline on GMP for radiopharmaceutical products should be used (3).

3. Glossary

The definitions given below apply to the terms used in this guideline. They may have different meanings in other contexts.

active pharmaceutical ingredient. With respect to radiopharmaceutical preparations, the active pharmaceutical ingredient is the radioactive molecule that is responsible for the radiopharmaceutical mechanism of action. This active pharmaceutical ingredient may be in the form of the radionuclide by itself, if its use by itself is clinically indicated, or in the form of a radionuclide coupled to a non-radioactive ligand or vector molecule.

as low as reasonably achievable. This term is used to define the principle of underlying optimization of radiation protection for occupational workers and the public, including patients. This is practised based on the principles of time, distance and shielding, while placing an emphasis on creating adequate awareness among all stakeholders.

clinical trial. Any systematic study on (radio)pharmaceutical products in human subjects, whether in patients or other volunteers, in order to discover or verify the effects of, or identify any adverse reaction to, investigational products; and to study the absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety.

Clinical trials are generally divided into phases I–IV, although phase IV studies usually do not apply to investigational radiopharmaceuticals, and thus are not mentioned further in this guideline. It is not always possible to draw clear distinctions between these phases, and different opinions about the details and methodology exist. However, the individual phases, based on their purposes as related to the clinical development of pharmaceutical products, can be briefly defined as follows:

- **Phase I.** These are the first trials for new radiopharmaceuticals (also called “first in human”), often carried out in healthy volunteers. Their purpose is to make a preliminary evaluation of safety, an initial pharmacokinetic and pharmacodynamic profile, and an initial safety assessment of the active ingredient and radiation dosimetry.
- **Phase II.** The purpose of studies in phase II is to determine activity and to assess short-term safety. The trials are performed in a limited number of subjects, but a greater number than in phase I, and aim to determine the optimal administered dose. In the case of therapeutic radiopharmaceuticals, they also aim to clarify the dose–response relationships in order to provide an optimal background for the design of extensive therapeutic trials.
- **Phase III.** This phase involves trials in large (and possibly varied) patient groups for the purpose of determining the short- and long-term safety and efficacy, and assessing the overall and relative diagnostic accuracy and therapeutic value of the intended radiopharmaceutical. Phase III studies are often multicentric. The pattern and profile of any frequent adverse reaction must be investigated and special features of the product must be explored (for example, clinically relevant drug interactions and factors leading to differences in effect, such as age). In general, the conditions under which the trials are conducted should be as close as possible to the normal conditions of use.

finished pharmaceutical product. With respect to radiopharmaceutical preparations, the finished pharmaceutical product is a combination of the active pharmaceutical ingredient and other components of the formulation such as diluents, radioprotectants and other formulation excipients. In some instances, the active pharmaceutical ingredient is co-produced concurrently with the finished pharmaceutical product in a single seamless process. In other cases, the active pharmaceutical ingredient is synthesized first and then formulated further as a separate process to yield the finished pharmaceutical product. In all cases, the finished pharmaceutical product is created once the active pharmaceutical ingredient is formulated in the final formulation form.

good manufacturing practices for radiopharmaceutical products. Good manufacturing practices (GMP) for radiopharmaceutical products are a set of practices, using a traceable process, that ensure that radiopharmaceutical products are consistently produced and controlled to the quality standards appropriate for their intended use and designed to consistently yield the radiopharmaceutical product. GMP fall under the umbrella of the overall quality management system.

investigational radiopharmaceutical. Any radiopharmaceutical product (new compound or a commercial product) being evaluated in a clinical trial.

investigator. The person responsible for the trial and for protecting the rights, health and welfare of the subjects in the trial. The investigator must be an appropriately qualified person, legally allowed to practice medicine or dentistry.

manufacturing or production. For the purpose of this document, these terms are defined in the same way as in the *IAEA/WHO guideline on good manufacturing practices for radiopharmaceutical products* (3). They refer to all the operations performed leading up to the finished pharmaceutical product, including the purchase of starting materials, production, quality control, release and storage of radiopharmaceuticals.

monitor. A person appointed by the sponsor who is responsible for monitoring and reporting the progress of the trial and for the verification of data.

order. An instruction to process, package and ship a certain number of doses of an investigational radiopharmaceutical.

preparation or kit reconstitution. For the purpose of this document, these terms are defined in the same way as in the *IAEA/WHO guideline on good manufacturing practices for radiopharmaceutical products* (3). They refer to all the procedures carried out as per instructions from marketing authorization holders that involve addition of radionuclide solution approved by regulatory authorities to an approved cold kit.

product specification file. A reference file containing all the information necessary to draft the detailed written instructions on processing, packaging, labelling, quality control testing, batch release, storage conditions and shipping.

protocol. A document that gives the background, rationale and objectives of the trial and describes its design, methodology and organization, including statistical considerations and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator or institution involved and the sponsor, and can, in addition, function as a contract.

radiopharmaceutical product. For the purpose of this document, this term is defined in the same way as in the *IAEA/WHO guideline on good manufacturing practices for radiopharmaceutical products* (3), as any pharmaceutical product that, when ready for use, contains one or more radionuclides (radioactive isotopes) included for medicinal purposes.

retention sample. An additional sample of the final drug product that is collected and stored for the purpose of being analysed, should the need arise.

sponsor. An individual, company, institution or organization that takes responsibility for the initiation, management and financing of a clinical trial. When an investigator independently initiates and takes full responsibility for a trial, the investigator also then assumes the role of the sponsor.

4. Quality management

- 4.1 There should be a comprehensively designed, clearly defined, documented and correctly implemented quality management system in place. Senior management should assume the responsibility for this, as well as for the quality of the investigational product.
- 4.2 All parts of the quality management system should be adequately resourced and maintained.
- 4.3 The quality management system should incorporate GMP, which should be applied to all stages of the product life cycle, including the transfer of technology and the interface between the manufacture and the trial sites (for example, with regard to shipment, storage and labelling).
- 4.4 The quality management system should ensure that:
 - products are designed and developed in accordance with the requirements of this document and other associated guidelines, such as good clinical practices, good laboratory practices, good storage and distribution practices, and GMP for radiopharmaceuticals, as appropriate (3–6);
 - responsibilities are clearly specified in job descriptions;
 - operations are clearly specified in a written form;
 - arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
 - all necessary controls on starting materials, intermediate products, bulk products and other in-process controls are in place;
 - calibrations and validations are carried out where necessary;
 - the finished radiopharmaceutical product is correctly processed and quality controlled according to the defined procedures;
 - there is an appropriate system for quality risk management;
 - satisfactory arrangements exist to ensure, as far as possible, that the investigational radiopharmaceuticals are stored, distributed and subsequently handled so that their quality is maintained;
 - deviations and changes are investigated and recorded with an appropriate level of root cause analysis done and appropriate corrective and preventive actions identified and taken.
- 4.5 For the manufacture of phase I and II radiopharmaceutical investigational products, the information on deviations, changes, out-of-specification investigations and corrective and preventative actions may be captured in a documentation system

that is less regimented than the standard operating procedures and forms that are normally used during manufacture of commercial radiopharmaceutical products where the degree of variability and reliability of the process has been established and validated. This less regimented documentation system allows for manufacturer flexibility, which is essential for the manufacture of the novel agent, as this process is inherently subject to a higher degree of variability when compared to agents in later stages of pharmaceutical development. Regardless of the documentation system utilized, the relevant information must be adequately captured and be traceable.

5. Quality risk management

- 5.1 A quality risk management system should cover a systematic process for the assessment, control, communication and review of risks to the quality of the product and, ultimately, to the protection of the trial subjects and patients (7). Specific areas of quality risk assessment should include:
 - sterility assurance;
 - expiration time;
 - method of sterilization;
 - mass of the drug substance or ligand;
 - physicochemical properties of the radionuclide or radiopharmaceutical;
 - planned dosing schedule (single dose or multiple doses into the same study subject);
 - route of administration;
 - agent specific in vitro stability;
 - the degree of clinical investigator supervision.
- 5.2 The quality risk management system should ensure that:
 - the evaluation of the risk is based on scientific knowledge and experience with the process and product, and is ultimately linked to the protection of the patient;
 - as the agent development continues, the basis of risk assessment is the transition from scientific knowledge and experience to process validation;
 - procedures and records for quality risk management system are retained;
 - the level of effort, formality and documentation of the quality risk management system process is commensurate with the level of risk.
- 5.3 The quality risk management system should be applied both proactively and retrospectively, when appropriate.

6. Personnel

- 6.1 There should be a sufficient number of appropriately qualified personnel available to carry out all the tasks for which the manufacturer of investigational products is responsible.
- 6.2 Individual responsibilities should be clearly defined, recorded as written descriptions and understood by all persons concerned.
- 6.3 A designated person, with experience in product development, clinical trial processes, and relevant guidelines on GMP and good clinical practices, should ensure that there are systems in place that meet the requirements of this guideline and other relevant GMP guidelines.
- 6.4 Personnel involved in the development, production and quality control of investigational products should be appropriately trained in relevant GMP and in the requirements specific to the manufacture of investigational radiopharmaceuticals.
- 6.5 The personnel should also be trained appropriately to prevent radiation contamination and other associated risks.
- 6.6 Production and quality control operations should be carried out under the control of clearly identified responsible persons who are separately designated and independent from one another.
- 6.7 In the manufacture of investigational radiopharmaceuticals, the same operator may be qualified as either a production operator or a quality control operator, or both, and the training for a specific function should be documented. Normally, the same operator should not perform both manufacture and quality control testing of the same batch of investigational radiopharmaceuticals. In circumstances where this may not be possible (for example, in academic radiopharmacies with limited personnel that are not engaged in the manufacture of investigational radiopharmaceuticals for phase I-II clinical evaluations on a routine daily basis, and where the produced investigational agent use is limited to the inside of the same institution), the same trained operator may perform both production and quality control testing, but it must be ensured that the batch release is performed by another independent authorized person.
- 6.8 In the manufacture of investigational radiopharmaceuticals, it may be possible for an authorized person responsible for batch release to also participate in either the batch production or quality control of a particular batch of an investigational radiopharmaceutical. However, if this authorized person does participate in either production or quality control testing of the particular batch, they cannot be responsible for the release of this batch of investigational radiopharmaceutical.

7. Documentation

- 7.1 Good documentation is an essential part of a quality management system. The documents should be appropriately designed, prepared, reviewed and distributed. They should also be appropriate for their intended use.
- 7.2 The documents (such as standard operating procedures, batch records and official reports) should be approved, signed and dated by the appropriate responsible person or persons. No authorized document should be changed without the prior authorization and approval of the responsible persons.
- 7.3 The documentation requirements applied during the manufacture of phases I-II investigational radiopharmaceuticals may be less vigorous than the documentation requirements applied during the manufacture of phase III investigational radiopharmaceuticals, but they would still need to be adequate to allow for traceability of the manufacturing process.

7.1 Specifications

- 7.4 Specifications (for starting materials, primary packaging materials, and intermediate, bulk and finished products), batch formulae and production instructions should be as precisely detailed as possible and should take into account the latest state of the art.
- 7.5 In developing specifications, attention should be paid to the characteristics that may affect the efficacy and safety of products, namely:
 - sterility and bacterial endotoxins
 - radioactive strength
 - radiochemical purity
 - specific activity, if applicable
 - batch size that is intended for the trial, where applicable
 - in-use stability
 - preliminary storage conditions
 - shelf-life of the product
 - appearance of the finished pharmaceutical product
 - radionuclidic purity, if applicable
 - chemical purity, if applicable.

- 7.6 As a result of the development of an investigational radiopharmaceutical, specifications may be changed by following a documented procedure. Changes should be authorized by a responsible person. Each new version should take into

account the latest data and information, current technology, and regulatory and pharmacopoeial requirements. There should be traceability to the previous version or versions. The reasons for any change should be recorded. The impact of the change on any ongoing clinical trial, product quality, stability, bioavailability or bioequivalence (where applicable) should be considered.

- 7.7 For phase II or III studies, information necessary to prepare the intended investigational radiopharmaceutical should be summarized in a product specification file, which contains reference to the relevant documentation (for example, standard operating procedures, qualification or validation protocols, analytical methods, stability data, or storage and shipment conditions) required to perform processing, packaging, quality control testing, batch release, labelling, storage conditions or shipping of the desired product.
- 7.8 The product specification file should indicate who has been designated or trained as the designated responsible person or persons for the release of batches.
- 7.9 The product specification files should be continuously updated, whilst, at the same time, ensuring the appropriate traceability to any previous versions.

7.2 Manufacturing formulae and processing instructions

- 7.10 Detailed manufacturing formulae, processing and packaging instructions and records should be available. Where this is not possible, other clear, written instructions and written records should be available for every manufacturing operation or supply.
- 7.11 These records should be used when preparing the final version of the documents to be used in routine manufacture.
- 7.12 Batch records should be retained for at least five years after the termination or discontinuance of the clinical trial or after the approval of the investigational radiopharmaceutical.
- 7.13 Where the data are intended for inclusion in an application for marketing authorization purposes, the records should be maintained until the end of the life cycle of the product.

7.3 Batch manufacturing records

- 7.14 Processing, packaging and testing records should be kept in sufficient detail for the sequence of operations to be accurately traced. They should contain any relevant remarks that increase the existing knowledge of the product, allow and reflect changes and improvements in the manufacturing operations, and justify the procedures used.

8. Premises

- 8.1 The premises where investigational radiopharmaceutical products are manufactured should be located, designed, constructed and maintained to suit the operations to be carried out. The design of the laboratories used for the handling of radioactive materials should always consider the need for radiation protection and compliance with “as low as reasonably achievable” standards, and should exhibit a high level of cleanliness and controls to minimize possible microbial contamination (8–10).
- 8.2 In cases where the same facility and equipment are used to prepare different radiopharmaceuticals, including investigational radiopharmaceuticals, the layout and design of premises should aim to minimize the risk of errors and mix-ups and permit effective cleaning and maintenance in order to avoid contamination, cross-contamination and, in general, any adverse effect on the quality of the products.
- 8.3 General technical requirements for the premises involved in the routine production of radiopharmaceuticals also apply in the case of investigational radiopharmaceuticals. For instance, drains should be avoided wherever possible and should not be present in cleanrooms. Where drains are required, these should be appropriately designed: sinks should be excluded from clean areas, and access points to technical areas (for example, rooms to access the rear of hot cells) should be configured in a way that minimizes entrance of maintenance and technical personnel to the production (clean) areas.
- 8.4 The heating, ventilation and air-conditioning system and pressure cascade for the different areas should be appropriately designed and maintained to minimize the risk of product contamination, and to protect personnel from the risk of radiation exposure. Pressure differentials should be monitored in areas of the facility where relative pressure differentials need to be maintained (such as cleanrooms where the quality of air is controlled) (11).
- 8.5 The facility must be equipped with appropriate radiation monitoring systems suitable for routine radioactive contamination monitoring for both areas and operators.
- 8.6 The appropriate controls should be in place to promote containment of radioactive gases and vapours. The premises must be equipped with an appropriate radioactive gas emission monitoring system.
- 8.7 Radioactive gases should be removed through separate air handling units fitted with the appropriate filters before being exhausted. These should be regularly checked for performance. The recirculation of potentially radiation-contaminated air should not be allowed.

- 8.8 A dedicated area and dedicated equipment should be used for the manufacture of any investigational radiopharmaceutical product involving human blood or plasma.
- 8.9 Quality control laboratories should be segregated from production areas.
- 8.10 The premises must be equipped with appropriately designed radioactive decontamination areas where operator decontamination may be carried out in compliance with approved protocols. At a minimum, these areas should be equipped with handwashing and eye washing stations.
- 8.11 The facility must be equipped with appropriately designed radioactive waste storage areas.

9. Equipment and utilities

- 9.1 Equipment and utilities should be selected, located, constructed and maintained to suit the operations to be carried out.
- 9.2 Equipment and utilities should be qualified for their intended use. This may include user requirement specifications, design qualification (if applicable), installation qualification, operational qualification and performance qualification. Equipment and devices, as appropriate, should be calibrated and maintained.
- 9.3 Equipment maintenance, qualification and calibration operations should be recorded and records should be maintained.
- 9.4 Computerized systems, such as those controlling equipment, should be verified to ensure they are reliable and fit for the intended purpose (12).
- 9.5 The dose calibrator (also known as the activity meter) should be qualified using suitable reference standards. If such a reference standard recognized by a national authority is not available, dose calibrator manufacturer recommendations or published literature may be used when deciding upon the appropriate dial setting.

10. Materials

10.1 Starting materials

- 10.1 The consistency of the production of investigational radiopharmaceutical products may be influenced by the quality of the starting materials. Their physical, chemical and, when appropriate, microbiological properties should therefore be defined, documented in their specifications, and controlled.

- 10.2 Specifications for precursors for radiolabelling should be as comprehensive as possible, given the current state of knowledge. They should include, for example, identity, purity or certification of origin (if applicable) and any other parameter or characteristic required to make the material suitable for its intended use.
- 10.3 Detailed information on the quality of precursors for radiolabelling and excipients (as well as of packaging materials) should be available.
- 10.4 Starting materials should be accepted by performing in-house testing. During the manufacture of investigational radiopharmaceuticals for phase I-II clinical trials, the in-house testing may also be in the form of a review of the certificate of analysis supplied by the reliable material supplier, to confirm compliance with the specification set by the investigational agent manufacturer. For positron emission tomography (PET) radiopharmaceuticals, the acceptance of materials based on review of the certificate of analysis may also apply to the phase III stage, as long as the final product release testing adequately confirms that materials of correct quality were used. For the manufacture of cold kit products, generators and therapeutic radiopharmaceuticals in phase III stages, additional physical tests (such as material identity confirmation) may need to be performed by the radiopharmaceutical manufacturer as part of the material acceptance process, in addition to a review of the certificate of analysis.

10.2 Reference standards for analytical purposes

- 10.5 Reference standards from reputable sources (such as qualified vendors) should be used, if available.
- 10.6 If not available from any source, the reference substance or substances for the precursor for radiolabelling should be prepared, fully characterized and released as reference materials by the producer of the investigational pharmaceutical product.

11. Production

- 11.1 Investigational radiopharmaceuticals intended for use in clinical trials should be manufactured at a facility that is specified in the investigational agent regulatory application.
- 11.2 Where activities are outsourced to contract facilities, the contract must then clearly state, *inter alia*, the responsibilities of each party, compliance with GMP or this guideline, and that the product or products to be manufactured or controlled are intended for use in clinical trials. Close cooperation between the contracting parties is essential.

- 11.3 Access to restricted areas should be by authorized and trained personnel only.
- 11.4 Processes should be designed to minimize the risk of contamination, cross-contamination and mix-ups. The following measures may be adopted to minimize these risks:
 - procedures for clearing the room of previous product materials;
 - processing and filling in segregated areas;
 - avoiding the manufacture of different products at the same time, either in the same dedicated space or by the same personnel;
 - performing manufacturing area decontamination and visual prechecks;
 - using manufacturing closed systems (such as automated systems), whenever possible;
 - using preassembled kit (cassettes), whenever possible.
- 11.5 The stability and shelf-life of the finished product should be defined following the execution of a suitable written protocol.
- 11.6 The expiration dates and times for radiopharmaceuticals should be based on the results of an adequate number of stability studies.

11.1 Manufacturing operations

- 11.7 As process knowledge of an investigational radiopharmaceutical is often not comparable with that of a radiopharmaceutical used for standard clinical care, process validation may not always be complete during the development phase of products; thus, critical quality attributes, process parameters and in-process controls should be identified, based on risk management principles and experience with analogous products, if available.
- 11.8 The necessary instructions for production should be defined and may be adapted based on the experience gained during radiopharmaceutical development itself.
- 11.9 For sterile investigational products, the controls to assure sterility of the final drug product should be no less than for licensed products (10). However, sterility verification studies (for example, bacteristasis or fungistasis) may not need to be conducted prior to pivotal phase III studies.

11.2 Packaging and labelling

- 11.10 At least the following information should be listed on the primary packaging container label (3):
 - name of the product and batch number

- name of the manufacturer
- route of administration
- amount of activity at calibration date and time in appropriate units
- volume
- where relevant, the international symbol for radioactivity
- cautionary statements (for example, “For clinical investigational use only”);
- the study or trial number.

Note: Reporting information about activity (“strength”) on the primary label may not always be possible due to radiation protection reasons. In this case, the information may be reported on the secondary packaging label.

- 11.11 In the absence of regulatory authority requirements, the following minimum information may be listed on the secondary packaging container label, in addition to any information listed on the primary packaging:
- the finished pharmaceutical product formulation composition
 - excipient information
 - storage instructions
 - address of the manufacturer, study sponsor, or investigator, as appropriate
 - radioactive concentration at calibration date and time, if applicable
 - end-of-synthesis date and time
 - expiration date and time
 - specific activity or mass.
- 11.12 The packaging must ensure that the investigational product remains in good condition during transport and storage. Any opening of or tampering with the outer packaging during transport should be readily discernible.

12. Quality control

- 12.1 Quality control should cover the sampling and testing of both the starting materials and the radiopharmaceutical final drug products, ensuring that materials are not released for use until their quality has been determined to conform to the predefined acceptance specifications.
- 12.2 As processes may not be standardized or fully validated, testing takes on more importance in ensuring that each batch meets the approved specification at the time of testing.

- 12.3 The release of a batch of an investigational radiopharmaceutical product should only occur after the designated responsible person has certified that the product meets the relevant batch release requirements. At a minimum, these requirements should include the following:
- a review and approval of batch records, including control reports, in-process test reports, changes, deviations and release reports demonstrating compliance with the product specification file, the order and protocol;
 - verification of appropriate production conditions;
 - verification of the quality of starting materials (for example, status of approval, certificate of analysis);
 - verification of the validation status of facilities, equipment, processes and methods, as appropriate;
 - verification of conditions of storage and shipment, if applicable;
 - verification of successful completion of quality control tests required for batch release.
- 12.4 Due to the inherent rapid radioactive decay of radiopharmaceuticals containing radionuclides with relatively short half-lives, these products may be released and administered prior to completion of all quality control testing. Under these circumstances, the required pre-release and post-release testing should be clearly defined and documented.
- 12.5 Sampling procedures should consider the nature and the characteristics of the material being sampled (for example, a small batch size or its radioactive content) to make sure that the samples are representative of the entire batch of radiopharmaceuticals.
- 12.6 Quality control samples should be prepared, handled and stored in a way that ensures the adequate identification and segregation of the test samples to avoid mix-ups and cross-contamination.
- 12.7 In the event that a finished radiopharmaceutical product batch fails to meet a release acceptance specification (that is, an out-of-specification event occurs), an investigation should be conducted and documented. During the investigation, the affected batch should be segregated and quarantined to prevent release. If the investigation confirms the out-of-specification result, the finished radiopharmaceutical product should be rejected. A confirmed out-of-specification event that is detected during post-release testing requires an immediate notification to the end clinician who has the drug product in their possession. A batch of finished radiopharmaceutical product involved in an out-of-specification

event may be released only if (a) the investigation reveals clear evidence that the obtained result is invalid; and (b) confirmatory testing results confirm the absence of non-compliance with the acceptance specifications. Final disposition confirming or invalidating the out-of-specification event should be notified to the clinician as quickly as possible.

- 12.8 Retention samples from every batch of a particular investigational radiopharmaceutical product should only be collected if they can be used to obtain meaningful testing data in the future. However, the collection of the retention samples is not required. The duration of storage of retention samples should be based on the ability to collect valid test data from using the sample.

13. Qualification and validation

- 13.1 The extent of qualification and validation activities should be in accordance with a risk-based approach, considering the complexity and critical aspects of the intended radiopharmaceutical production.
- 13.2 The extent of qualification and validation required for the manufacture of investigational radiopharmaceuticals in phase I-II trials may be less than for the manufacture of investigational radiopharmaceuticals in pivotal phase III trials. Nevertheless, the critical characteristics of the investigational radiopharmaceutical should always be addressed. For example, critical manufacturing step in-process control parameters, such as reaction temperatures or transfer of the activities, may need to be defined and monitored at any stage of development; on the other hand, the validation of less critical controls, such as bioburden sample collection or determination of maximum in-process holding times, may not be required during phases I-II.
- 13.3 The facilities and equipment need to be properly maintained and calibrated at any stage of development.
- 13.4 Equipment should be qualified for its intended use. At a minimum, the equipment should be verified to be in conformance with the preventive maintenance and operational qualification requirements of the equipment manufacturer, as well as the performance qualification requirements of the investigational radiopharmaceutical manufacturer, as applicable.
- 13.5 The validation of aseptic investigational radiopharmaceutical production procedures presents special problems, as the batch size is often very small and the number of units filled may be not adequate for a full validation protocol. Thus, the validation of aseptic procedures needs to be supported by an operator

and process validation via a media fill test, which consists of conducting a process simulation using broad spectrum bacterial growth media to demonstrate that the aseptic processing, controls and production environment are capable of producing a sterile product. The successful completion of media fill testing is a prerequisite for the clinical production of investigational radiopharmaceuticals at any stage of development.

- 13.6 Manufacturing process validation should only be carried out after all of the critical requirements (for example, media fill testing, relevant standard operating procedures for operator training, and preventive maintenance and operational qualification of equipment) have been completed. The validation batches campaign should include an adequate number of batches of the intended radiopharmaceutical(s). The number of batches and the batch size range should be predetermined as part of a risk assessment performed prior to process validation. In general, the completion of a minimum of three consecutive batches aimed for validation and stability studies is sufficient for the purposes of completing manufacturing process validation in phase I trials. However, the number of batches produced may need to be increased in certain situations. For example, more validation and stability runs may be required when the manufacturer is trying to qualify multiple suppliers of a particular critical component (such as radionuclide provided by multiple suppliers).
- 13.7 Defined, documented and reproducible analytical methods aimed to establish chemical, radiochemical and radionuclidic purity, as well as identity, specific activity (if applicable) and impurities content, should be established before any manufacture for human subjects begins. However, analytical method validation protocols fully compliant with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) standards (13) for validation may be generated and implemented as part of the transition into pivotal phase III trials.
- 13.8 Compendial analytical methods applied by the investigational radiopharmaceutical manufacturer that are described in relevant pharmacopeia do not require validation but may require verification prior to the initiation of manufacture for pivotal phase III trials. For example, the compendial endotoxin testing method may not require full analytical method validation as described in relevant ICH guidances but may require the verification via conduct of specific inhibition and enhancement studies of the finished pharmaceutical product.
- 13.9 General principles on validation of analytical procedures may be followed (13); however, the unique nature of radioactivity should be considered and specific adaptations should be made, where required.

14. Complaints

- 14.1 There should be a written procedure describing the management of complaints. The procedure should provide a clear and concise description of responsibilities, actions that may need to be undertaken, communication pathways and structure, traceability and reporting requirements in the event that a complaint is received.
- 14.2 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated.
- 14.3 Where necessary, the appropriate follow-up action, possibly including product recall, should be taken after the investigation and evaluation of the complaint.
- 14.4 All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
- 14.5 Any potential impact on the trial or on the product development should be investigated in order to determine the cause and take any necessary corrective action.

15. Recalls

- 15.1 There should be a written procedure describing the management of a recall of an investigational radiopharmaceutical. The procedure should provide a clear and concise description of responsibilities, actions that may need to be undertaken, communication pathways and structure, traceability and reporting requirements in the event a product recall is initiated.
- 15.2 The recall of a product should be documented and inventory records should be kept.
- 15.3 Multiple project-specific and product recall procedures may need to be implemented for various radiopharmaceuticals in order to reflect the requirements for a specific project. For example, the product recall requirements for a manufacturer that supplies investigational agents to the clinic within the same institution or hospital may differ significantly from the manufacturer that works with a pharmaceutical company sponsor and distributes the manufactured product to multiple external clinics. In all cases, the exact requirements need to be clearly defined and the staff need to be trained on those specific requirements.

16. Returns

- 16.1 Investigational radiopharmaceuticals should be returned under the agreed conditions defined by the sponsor, specified in written procedures and approved by authorized staff members.
- 16.2 Return processes should be in accordance with the handling of radioactivity and radiation protection rules.
- 16.3 Inventory records of returned products should be kept.
- 16.4 Returned radiopharmaceuticals should not be reused.
- 16.5 Since the return of radioactive products is often not practical, the main purpose of recall procedures for radiopharmaceutical products should be to prevent their use, rather than an actual return. If necessary, the return of radioactive products should be carried out in accordance with national and, where applicable, international transport regulations (14).

17. Shipping

- 17.1 The shipping of investigational radiopharmaceuticals should be carried out in accordance with written procedures laid down in the protocol or shipping order given by the sponsor.
- 17.2 Shipping processes should also be in accordance with international and local rules (14).
- 17.3 The shipment should be accompanied by a printed form, including the relevant information related to the investigational radiopharmaceutical (for example, the same information included in the secondary packaging label).

18. Destruction

- 18.1 The activity of the active principle of investigational radiopharmaceuticals decreases following the decay law and half-life of the radionuclide; thus, usually there is no need for product destruction.
- 18.2 Should the product be destroyed, however, international and local rules on handling radioactivity and radiation protection should be followed. A dated certificate of, or receipt for, destruction should be provided to the sponsor. These documents should clearly identify or allow traceability of the batches and patient numbers involved and the actual quantities destroyed.

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Further reading

- International Ethical Guidelines for Health-related Research Involving Humans Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), Geneva, 2016. Geneva: CIOMS; 2016 (<https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf>, accessed 17 August 2022).
- The International Pharmacopoeia. Geneva: World Health Organization; updated regularly (<https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/international-pharmacopoeia>).
- EudraLex – Volume 4 – Good Manufacturing Practice (GMP) guidelines. EU Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC and 91/412/EEC (https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-4_en, accessed 17 August 2022).
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4. Related guidelines

4.1 WHO good practices for research and development facilities of pharmaceutical products

Annex 6, WHO Technical Report Series, 1044,
2022 (new)

Background

In view of the need for the development of health products, including research and development for the treatment of COVID-19 therapies, the World Health Organization (WHO) Prequalification Team – Inspection Services (PQT/INS) raised the urgency for the development of life cycle-appropriate good practices text to address the manufacturing of developmental batches, pilot batches and the sequential stability data that are submitted in product applications (dossiers) for marketing authorization and the prequalification of medical products.

There is currently no other specific WHO guideline that addresses this matter. The data collected from these batches influence the following aspects of the product:

- stability
- process validation
- analytical method development and validation.

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1. Introduction

- 1.1 With an ever-increasing awareness of the risks in pharmaceutical production and control and the life cycle approaches being followed, greater emphasis is being placed on ensuring that the research and development of products are appropriately controlled and documented.
- 1.2 Consequently, it is necessary that manufacturers of pharmaceutical products are able to submit all relevant data and information related to their development, including the facilities used, the experimental designs employed in the validation of manufacturing processes, and quality control procedures, to the regulators, where required, for review. This is to ensure that the facilities, quality systems, data and information meet the appropriate standards and applicable good practices.
- 1.3 This document intends to provide guidance on good practices to research and development facilities. It further aims to ensure that the correct systems are followed, ensuring appropriateness, reliability and the quality of products, processes, procedures and data. This further helps to ensure that products meet the requirements for safety, efficacy and quality that they purport to possess.
- 1.4 In addition to product development, other activities – including the production of pilot-scale batches, process validation, cleaning procedure development, cleaning validation studies, and stability studies – are often undertaken in such facilities.
- 1.5 The World Health Organization (WHO) document *WHO good manufacturing practices for investigational products* (1) specifically addresses the requirements and recommendations for products used in clinical trials. Other WHO guidelines address specific requirements and recommendations, including data integrity, stability testing, analytical method validation, cleaning validation and technology transfer (see references and further reading sections at end of document).
- 1.6 This document should be read in conjunction with other WHO guidelines on good manufacturing practices (GMP), where appropriate and where applicable, as referenced in the relevant documents (2–14). Other documents of interest are listed under the section on further reading following the reference list.

2. Scope

- 2.1 This guideline is specifically applicable to research and development facilities of pharmaceutical products, procedures, processes and data that are intended for transfer and submission for approval in marketing authorization applications, process validation, technology transfer-related activities (15), validation (7),

quality control laboratory activities such as stability testing and development (16), and validation of cleaning procedures (see Figure 1 and section 4 below).

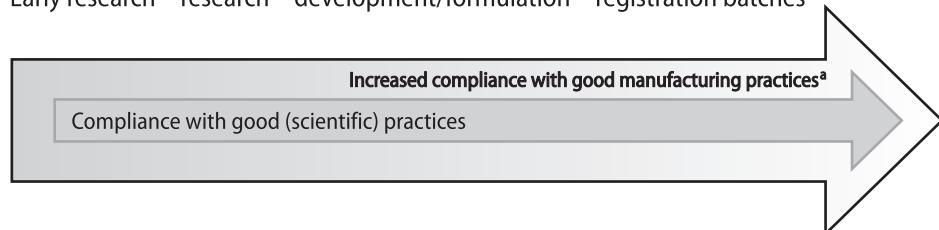
- 2.2 The main focus of this document is to provide guidance on good practices in the production and control of preclinical and not-for-human-use batches, manufactured in pharmaceutical formulation and development facilities, where these are directly supporting (for example) shelf-life claims, animal studies or validation activities. The principles described in this document may be applied in facilities where other products, such as biopharmaceutical products, vaccines and medical devices, are manufactured.
- 2.3 This guide excludes whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), medicinal gases, radiopharmaceuticals and gene therapy products.
- 2.4 The sections below are to be considered general guidance and may be adapted to meet individual needs. The effectiveness of alternative approaches, however, should be demonstrated.
- 2.5 In this guide, the term “should” indicates recommendations that are expected to apply unless they are shown to be not applicable or can be replaced by an alternative demonstrated to be acceptable.
- 2.6 This guide, as a whole, does not cover safety aspects for the personnel engaged in the research and development or the aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.
- 2.7 This guide is not intended to define registration requirements or modify pharmacopoeial requirements or other guideline recommendations. For details on process development, it is recommended that other guidelines, such as those published by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), be read in conjunction with this document.
- 2.8 This guide does not affect the ability of the responsible regulatory agency to establish specific registration or filing requirements. All commitments in registration and filing documents must be met. This document provides information to consider for a risk- and science-based approach in the research and development of pharmaceutical products.
- 2.9 Due to the nature of development work, and an increasing expectation for compliance with standards in manufacture, the guidance in this document would normally be applied based on risk assessment, in an increasing manner,

from development to commercial batch manufacturing. The application of good practices in research and development should increase as the process proceeds from early development work to the final steps of development and formulation, stability testing, process validation and cleaning validation.

Fig. 1

Application of this guideline

Early research – research – development/formulation – registration batches



^a The principles described in this guideline are applied, based on risk management principles, in an increased manner from early research to development to registration batches.

3. Glossary

The definitions given below apply to the terms used in this guideline. They have been aligned as much as possible with the terminology in related WHO guidelines and good practices and included in the WHO *Quality Assurance of Medicines Terminology Database: list of terms and related guideline*,¹ but may have different meanings in other contexts.

batch (or lot). A defined quantity of starting material, packaging material or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches that are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

batch records. All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

¹ https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/mqa-terminology-sept-2020.pdf?sfvrsn=48461fc_5.

bulk product. Any product that has completed all processing stages, usually not including final packaging and labelling.

calibration. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

cleanability. The factors that impact the ability to remove a residue from surfaces, including material of construction, the solubility of the material in different agents and the matrix of the material being cleaned.

cleaning verification. The act of demonstrating that cleaning was done to an acceptable level, for example, between two batches.

contamination. The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.

finished product. A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling.

in-process control. Checks performed during production in order to monitor and, if necessary, adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

intermediate product. A partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

knowledge management. Systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components.

manufacture/manufacturing. Includes all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage, distribution and related controls.

manufacturer. A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

marketing authorization (product licence, registration certificate). A legal document issued by the competent medicines regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life.

master formula. A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product, as well as the processing instructions, including the in-process controls.

master record. A document or set of documents that serves as a basis for the batch documentation (blank batch record).

packaging. All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product. The filling of a sterile product under aseptic conditions, or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

packaging material. Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

pharmaceutical product. Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state. (Note: In this guidance, the term pharmaceutical product may include products for preclinical use.)

production. All operations involved in the preparation of a pharmaceutical product, from receipt of materials through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

qualification. Documented evidence that premises, systems or equipment are able to achieve the predetermined specifications, are properly installed, and/or work correctly, and lead to the expected results.

quality audit. An examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors.

quality risk management. A systematic process for the assessment, control, communication and review of risks.

specification. A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

standard operating procedure. An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (for

example, equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain standard operating procedures may be used to supplement product-specific master and batch production documentation.

starting material. Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

validation. The action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results.

4. Quality management

- 4.1 There should be a quality management system encompassing adequate resources, a written organizational structure and procedures to follow.
- 4.2 All parts of the quality management system should be adequately resourced and maintained, including with sufficient competent personnel, suitable premises, equipment and facilities. The necessary resources should include:
 - a sufficient number of appropriately qualified, trained personnel
 - adequate premises and space
 - suitable equipment and services
 - appropriate materials, containers and labels
 - suitable storage and transport.
- 4.3 Roles, responsibilities and authorities should be defined, communicated and implemented.
- 4.4 The quality system should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.
- 4.5 Initial research, as well as development activities, should be defined and documented. Development activities, including initial research, should be adequately documented. Controls should be commensurate with the stage of product development – that is, for testing options or at a final stage for further use where the guideline on *WHO good manufacturing practices for investigational products* applies (1).
- 4.6 The quality system should ensure, as applicable and according to the stage of research and development, that:

- managerial responsibilities are clearly specified in job descriptions;
 - personnel are trained;
 - instructions and procedures are written in clear and unambiguous language, and followed;
 - procedures are correctly carried out;
 - records are made (manually or by recording instruments) during production and testing;
 - records are maintained;
 - there is a system for quality risk management that is applied, as appropriate;
 - arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
 - all necessary controls on starting materials, intermediate products, bulk products and other in-process controls are carried out;
 - calibrations and validations are carried out, where appropriate;
 - the product and process knowledge is managed;
 - products are designed and developed in accordance with applicable good practices, as appropriate;
 - development procedures are documented;
 - cleaning procedures are developed, verified and validated, where appropriate;
 - stability testing is done following written procedures and protocols;
 - data meet ALCOA+ (attributable, legible, contemporaneous, original and accurate) requirements, where applicable.
- 4.7 There should be a periodic management review with the involvement of senior management.

5. Quality risk management

- 5.1 A system of quality risk management should be implemented. The system should ensure that risks are identified based on scientific knowledge and experience. The appropriate controls should be identified and implemented to mitigate risks.
- 5.2 The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk and the stage from research to development, to commercial batch manufacturing and control (see Figure 1).
- 5.3 Systems should be in place to manage and minimize the risks inherent in research and development.

6. Sanitation and hygiene

- 6.1 Procedures should be implemented to maintain sanitation and hygiene. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, and products for cleaning and disinfection.
- 6.2 Potential sources of contamination should be identified and controlled.

7. Qualification and validation

- 7.1 Where qualification and validation are performed, the scope and extent should be appropriate using a risk-based approach.
- 7.2 The qualification and validation policy and approach should be defined and documented, for example, in a validation master plan.
- 7.3 Where qualification and validation are carried out, the responsibility for performing validation should be clearly defined.
- 7.4 Where process validation, cleaning validation and analytical procedure validation are done as a part of development, procedures and protocols should be followed. Reports should be available and retained.

8. Outsourced activities

- 8.1 Outsourced activities should be correctly defined, agreed and controlled through a written agreement.
- 8.2 All responsibilities and arrangements for activities, such as quality control (QC) testing and technology transfer, should be clearly described.

The contract giver

- 8.3 The contract giver is responsible for assessing the suitability and competence of the contract acceptor to successfully carry out the work or tests required and for approval of the contract activities.
- 8.4 The contract giver should provide the contract acceptor with all the information necessary to carry out the contracted operations correctly.
- 8.5 The contract giver should ensure that the contract acceptor is fully aware of any hazards associated with the product, work or tests.
- 8.6 The contract giver should review and assess relevant records and results related to the outsourced activities.

- 8.7 The contract giver is responsible for ensuring that the contract acceptor understands that its activities may be subject to inspection by the competent authorities.

The contract acceptor

- 8.8 The contract acceptor must have adequate premises, equipment, knowledge, experience, and competent, trained personnel to satisfactorily carry out the work ordered by the contract giver.
- 8.9 The contract acceptor should not pass to a third party any of the work entrusted under the contract without the contract giver's prior evaluation and approval of the arrangements.
- 8.10 The contract acceptor should agree to a period of time for retention of documents and data prior to archival or returning to the contract giver.

The agreement

- 8.11 The technical aspects of the agreement should be drawn up by competent persons suitably knowledgeable in the field of law, research, development and good practices.
- 8.12 The agreement should define the roles and responsibilities of all parties.
- 8.13 The agreement should permit the contract giver to audit the facilities and activities of the contract acceptor.

9. Self-inspection and quality audits

- 9.1 There should be a written self-inspection programme.
- 9.2 Self-inspection should be performed routinely and may, in addition, be performed on special occasions.
- 9.3 The team responsible for self-inspection should consist of personnel with the appropriate knowledge and experience, free from bias.
- 9.4 Self-inspection should cover at least the following items, where appropriate:
- personnel
 - premises, including personnel facilities
 - maintenance of buildings and equipment
 - storage of starting materials and finished products
 - equipment
 - production and in-process controls

- QC
 - documentation
 - data and data integrity
 - sanitation and hygiene
 - qualification and validation
 - calibration of instruments or measurement systems
 - control of labels
 - results of previous self-inspections and any corrective steps taken.
- 9.5 The outcome of the self-inspection should be documented. Corrective actions and preventive actions should be identified and implemented within a defined timeline. There should be an effective follow-up programme.
- 9.6 Self-inspections may be supplemented by independent quality audits.

10. Personnel

- 10.1 Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.
- 10.2 All personnel should be aware of the principles of this guideline and other applicable good practices (GxP).
- 10.3 Steps should be taken to prevent unauthorized people from entering storage, production and QC areas.
- 10.4 Smoking, eating, drinking, chewing and keeping plants, food, drink, smoking material and personal medicines should not be permitted in any area where they might adversely influence product quality.
- 10.5 The appropriate protective garments should be worn, based on operation performed and risk.
- 10.6 Personnel who are ill should not engage in the manufacture of pharmaceutical products.

11. Training

- 11.1 Training should be provided in accordance with a written programme that covers topics such as the theory and practice of GMP and the duties assigned. The appropriate task-related training should be further provided based on technical requirements and activities undertaken.

- 11.2 The effectiveness of training should be assessed.
- 11.3 Training and assessment records should be kept.
- 11.4 Where appropriate, specific training should be given on the handling and segregation of highly active, toxic, infectious or sensitizing materials and the need for separate, dedicated facilities where these are required.

12. Premises

- 12.1 Premises should be located, designed, constructed, adapted and maintained to suit the operations to be carried out.
- 12.2 The layout and design should aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid build-up of dust or dirt and, in general, any adverse effect on the products and activities.
- 12.3 The premises should be cleaned according to detailed procedures. Records should be maintained.
- 12.4 The electrical supply, lighting, temperature, humidity and ventilation should be appropriate.
- 12.5 Toilets and rest and refreshment rooms should be separate from production and control areas.
- 12.6 Storage areas should be of sufficient capacity, with proper separation and segregation of materials.
- 12.7 Storage areas should be clean and dry and should be designed or adapted to ensure that the required storage conditions are maintained. Conditions should be controlled, monitored and recorded, where appropriate.
- 12.8 Certain materials, such as highly active radioactive materials and narcotics, should be stored in safe and secure areas.
- 12.9 Materials identified for testing should be sampled and analysed.
- 12.10 The stages in production, including weighing, compounding, and packaging, should be done in a manner that prevents contamination and mix-ups.
- 12.11 QC areas should be designed to suit the operations to be carried out in them. There should be sufficient space, instruments, and equipment, and the appropriate reference materials, solvents and reagents.

12.12 Poisons, pesticides and hazardous materials should not be stored or used in product manufacturing areas.

13. Equipment and instruments

- 13.1 The equipment and instruments should be located, designed, constructed, adapted and maintained to suit the operations to be carried out. They should allow for effective cleaning and maintenance in order to avoid a build-up of dust or dirt.
- 13.2 Pipework, instruments and devices should be adequately marked.
- 13.3 Measuring equipment should be available for production and control operations and, where necessary, should be calibrated, verified and serviced on a scheduled basis. Records should be maintained.
- 13.4 The equipment and instruments should be thoroughly cleaned on a scheduled basis.
- 13.5 Defective equipment and instruments should be removed from operational areas or be clearly labelled as defective in order to prevent use.

14. Materials

- 14.1 Materials should be purchased from suitable suppliers.
- 14.2 Where so identified, materials should be quarantined immediately after receipt, sampled and tested.
- 14.3 Materials should be used within their shelf-life.
- 14.4 Materials should be stored under the appropriate conditions, as specified on their labels, and in an orderly fashion to permit segregation.
- 14.5 The dispensing of materials for the production of a batch should be recorded. Materials should be accurately weighed or measured into clean and properly labelled containers.
- 14.6 No materials used for operations, such as cleaning, the lubrication of equipment or pest control, should come into direct contact with the product. Where possible, such materials should be of a suitable grade (for example, food grade) to minimize health risks.
- 14.7 All materials, including water, should be suitable for its intended use.

- 14.8 Packaging and printed materials should be stored in secure conditions so as to exclude the possibility of unauthorized access.
- 14.9 Intermediate and bulk products should be kept under appropriate conditions.
- 14.10 Finished products should be stored under suitable conditions and appropriately segregated.
- 14.11 Rejected materials and products should be clearly marked as such. They should be handled in an appropriate and timely manner. Whatever action is taken should be approved by authorized personnel and recorded.
- 14.12 Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed containers, and as required by national legislation.
- 14.13 All waste materials should be stored in a safe manner and disposed of at regular intervals to avoid accumulation.

15. Documentation

- 15.1 Documentation includes procedures for materials and methods of production and control. The design and use of documents depend upon the research and development facility.
- 15.2 Documents should be designed, prepared, reviewed and authorized for use.
- 15.3 Standard operating procedures should be reviewed periodically and kept up to date. Superseded documents should be retained for a defined period of time.
- 15.4 Entries of data and information should be clear and legible and meet ALCOA+ principles, as applicable.
- 15.5 GxP data (including records for storage) may be recorded by electronic data-processing systems or by photographic or other reliable means. Batch production and control records should be protected throughout the defined period of retention.
- 15.6 Labels should be clear and unambiguous, and in the company's agreed format.
- 15.7 There should be appropriately authorized and dated specifications, including tests on identity, purity and quality, for starting materials and for finished products, as appropriate.
- 15.8 Pharmacopoeias, reference standards, reference spectra and other reference materials should be available, where applicable.

- 15.9 Specifications should contain appropriate information, such as the designated name, internal code reference, and qualitative and quantitative requirements, with acceptance criteria. Other data may be added to the specification.
- 15.10 The packaging material should be examined for compliance with the specification, as appropriate.
- 15.11 Specifications for intermediate and bulk products should be available where the need has been identified, as appropriate.
- 15.12 Specifications for finished products should be available and include the required information, where available.
- 15.13 A master formula or batch recipe, containing the relevant information, should be available for the product and batch size.
- 15.14 Packaging instructions should exist for the products to be packed.
- 15.15 A batch processing record should be kept for each batch processed.
- 15.16 During processing, detailed information should be recorded at the time each action is taken. Upon completion, the record should be dated and signed by the person responsible in accordance with data integrity expectations.
- 15.17 A batch packaging record should be kept for each batch packed.
- 15.18 Standard operating procedures and corresponding records, where required, should be available. These include:
 - equipment assembly and cleaning
 - personnel training, clothing and hygiene
 - maintenance
 - sampling
 - analytical apparatus and instrument calibration
 - testing
 - rejection
 - pest control.
- 15.19 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues and labels or documents not required for the current operation.

16. Processing and process design

Processing

Note: For more details on specific aspects relating to process development, see ICH guidelines Q8 and Q11 (17, 18).

- 16.1 The selection of the starting materials and manufacturing process should be carefully considered in order to ensure that the intended product will meet the intended standards of safety, efficacy and quality in a consistent manner.
- 16.2 Knowledge management and risk assessment principles should be applied. Quality attributes, critical quality attributes, process parameters and critical process parameters should be defined and documented once sufficient data are available.
- 16.3 The design of experiments should cover identified variables.

Process design

Note: For details on process validation, see WHO Technical Report Series No. 1019, Annex 3, Appendix 7, 2019 (10) as well as European Union and United States Food and Drug Administration guidelines (19, 20).

- 16.4 Process design – often referred to historically as “prospective validation” – is usually initiated by research and development facilities.
- 16.5 Process design should normally cover the design of experiments, process development, the manufacture of products for use in clinical trials, pilot-scale batches and technology transfer.
- 16.6 Process design should be verified during product development. Process design should cover such aspects as the selection of materials; consideration for expected impurities; expected production variation; selection of production technology or process and qualification of the unitary processes that form the manufacturing process as a whole; selection of in-process controls; tests; inspection; and its suitability for the control strategy.
- 16.7 Where the validation data are intended to be used in applications for marketing authorization, all batch data, results and related information should be clear, detailed and in compliance with ALCOA+.

17. Quality control

- 17.1 There should be adequate resources available to ensure that all the QC arrangements are effectively and reliably carried out.

17.2 Activities and responsibilities of the QC unit include:

- sampling and testing (for example, starting materials, packaging materials, intermediate products, bulk products and finished products);
- performing the necessary qualification and validation;
- evaluating, maintaining and storing reference materials;
- ensuring that the stability programme and testing are carried out;
- conducting environmental monitoring.

17.3 The appropriate records should be kept, demonstrating that all the required activities were performed.

17.4 Sufficient samples of materials and products should be retained for a defined period of time.

17.5 The appropriate reference standards (official, secondary or working standards) should be used. Standards should be stored in an appropriate way.

17.6 Whenever official reference standards exist, these should preferably be used.

17.7 Where secondary and working standards are established and used, these should be tested at regular intervals to ensure that they are fit for their intended use.

17.8 Reference standards should be appropriately labelled with at least the following information:

- name of the material
- batch or lot number and control number
- date of qualification
- requalification date
- potency
- storage conditions.

18. Stability studies

Note: See guideline on stability testing of active pharmaceutical ingredients and finished pharmaceutical products, WHO Technical Report Series No. 1010, Annex 10, 2018 (11).

18.1 Where stability determination is initiated by research and development organizations, a written programme should be developed and implemented to include such elements as:

- a complete description of the product involved in the study;
- the complete set of testing procedures, parameters and limits;
- attributes such as potency or assay, degradation products and physical characteristics;
- evidence that these tests indicate stability;
- the testing schedule for each product;
- provision for special storage conditions;
- provision for adequate sample retention.

18.2 Sampling should be done in accordance with written procedures.

18.3 Sample preparation and testing procedures should be detailed and followed. Any deviations from the procedures should be clearly documented.

18.4 The results and data generated should be documented and should include the evaluation and the conclusions of the study.

18.5 Where stability data are intended to be used in applications for marketing authorizations, all batch data, results and related information should be clear, detailed and in compliance with ALCOA+.

18.6 Records should be maintained for a defined period of time.

19. Analytical procedure development

19.1 Analytical procedures developed by research and development organizations should be appropriately documented in sufficient detail to facilitate their successful transfer, when required.

19.2 Analytical procedures should be appropriately validated, where required, as fit for purpose.

Note: For details on analytical procedure validation, see WHO Technical Report Series No. 1019, Annex 3, Appendix 4, 2019 (12).

20. Technology transfer

Note: For details on technology transfer, see WHO Technical Report Series No. 1044, Annex 4, 2022 (15).

20.1 Development work, including programmes, procedures, protocols, specifications, process design and validation from research and development facilities, may be transferred to commercial manufacturing and QC sites.

- 20.2 Data and information relating to equipment, instruments, manufacturing and testing should be at an appropriate level of detail, traceable and available.
- 20.3 Authorized procedures should be followed when transferring technology from research and development organizations to commercial manufacturing and QC facilities.

21. Life cycle approach

- 21.1 Industry should implement policies and procedures that will encourage science-based and risk-based approaches in product research and development.
- 21.2 Continual improvement should be encouraged across the entire product life cycle.
- 21.3 Knowledge gained from the commercial manufacturing of a product, as well as knowledge gained from other products, can be used to further improve process understanding and process performance.
- 21.4 New technologies and the review and interpretation of statistical evaluation of results from process design, validation and other processes, as well as other applicable data and information, should be considered in order to encourage continual improvement during the process development stage of the life cycle of the product.
- 21.5 Where appropriate, these should be shared and transferred to commercial manufacturing facilities.

22. Cleaning procedure development, cleaning verification and cleaning validation

Note: For details on cleaning validation, see WHO Technical Report Series No. 1019, Annex 3, Appendix 3, 2019, and the WHO points to consider when including health-based exposure limits (HBELs) in cleaning validation, WHO Technical Report Series No. 1033, Annex 2, 2021 (13, 14).

- 22.1 Research and development facilities may be involved in the development and validation of cleaning procedures. quality risk management principles should be applied in cleaning procedure development and cleaning validation.
- 22.2 The development of cleaning procedures should include cleanability.
- 22.3 Where preparatory work for cleaning validation is done in research and development facilities with a view to technology transfer, consideration should be given to HBELs in the approach.

- 22.4 The sampling of procedures should include swab samples and rinse samples, where appropriate. Maximum safe residue, maximum safe surface residue and visible residue limits should be considered in the cleaning validation approach.
- 22.5 The development of the analytical procedures to be used in the testing for residues should be appropriately documented. The procedures should be validated.
- 22.6 The procedures for sampling and testing, and the results obtained, should meet ALCOA+ principles. The data and information should be retained over the life cycle of the product.
- 22.7 Procedures and protocols should be followed for the technology transfer to commercial manufacturing sites.
- 22.8 Records should be maintained.

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4.2 WHO guidelines for drafting a site master file¹

Annex 14, WHO Technical Report Series, 961,
2011

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¹ Based on the *Explanatory notes for pharmaceutical manufacturers on the preparation of a site master file* of the Pharmaceutical Inspection Convention.

1. Introduction

- 1.1 The site master file (SMF) is prepared by the pharmaceutical manufacturer and should contain specific information about the quality management policies and activities of the site, the production and/or quality control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of a pharmaceutical operation is carried out on the site, an SMF need only describe those operations, e.g. analysis, packaging, etc.
- 1.2 When submitted to a regulatory authority, the SMF should provide clear information on the manufacturer's good manufacturing practices (GMP)-related activities that can be useful in general supervision and in the efficient planning and undertaking of GMP inspections.
- 1.3 An SMF should contain adequate information but, as far as possible, not exceed 25–30 pages plus appendices. Simple plans, outline drawings or schematic layouts are preferred instead of narratives. The SMF, including appendices, should be readable when printed on A4 paper sheets.
- 1.4 The SMF should be a part of documentation belonging to the quality management system of the manufacturer and kept updated accordingly. The SMF should have an edition number, the date it becomes effective and the date by which it has to be reviewed. It should be subject to regular review to ensure that it is up to date and representative of current activities. Each annex can have an individual effective date, allowing for independent updating.

2. Purpose

The aim of these explanatory notes is to guide the manufacturer of medicinal products in the preparation of an SMF that is useful to the regulatory authority in planning and conducting GMP inspections.

3. Scope

These explanatory notes apply to the preparation and content of the SMF. Manufacturers should refer to regional and or national regulatory requirements to establish whether it is mandatory for manufacturers of medicinal products to prepare an SME.

These explanatory notes apply for all kinds of manufacturing operations such as production, packaging and labelling, testing, relabelling and repackaging of all types of medicinal products. The outlines of this guide could also be used in the preparation of an

SMF or corresponding document by blood and tissue establishments and manufacturers of active pharmaceutical ingredients (APIs).

4. Content of site master file

Refer to the Appendix for the format to be used.

Appendix

Content of a site master file

1. General information on the manufacturer

1.1 Contact information on the manufacturer

- name and official address of the manufacturer;
- names and street addresses of the site, buildings and production units located on the site;
- contact information of the manufacturer including 24-hour telephone number of the contact personnel in the case of product defects or recalls; and
- identification number of the site as e.g. global positioning system (GPS) details, D-U-N-S (Data Universal Numbering System) number (a unique identification number provided by Dun & Bradstreet) of the site or any other geographical location system.

1.2 Authorized pharmaceutical manufacturing activities of the site

- copy of the valid manufacturing authorization issued by the relevant competent authority in Annex 1; or when applicable, reference to the EudraGMP database. If the competent authority does not issue manufacturing authorizations, this should be stated;
- brief description of manufacture, import, export, distribution and other activities as authorized by the relevant competent authorities including foreign authorities with authorized dosage forms/activities, respectively; where not covered by the manufacturing authorization;
- type of products currently manufactured on-site (list in Annex 2) where not covered by Annex 1 or the EudraGMP database; and
- list of GMP inspections of the site within the last five years; including dates and name/country of the competent authority having performed the inspection. A copy of the current GMP certificate (Annex 3) or reference to the EudraGMP database should be included, if available.

1.3 Any other manufacturing activities carried out on the site

- description of nonpharmaceutical activities on site, if any.

2. Quality management

2.1 The quality management system of the manufacturer

- brief description of the quality management systems run by the company and reference to the standards used;
- responsibilities related to the maintaining of the quality system including senior management; and
- information on activities for which the site is accredited and certified, including dates and contents of accreditations, and names of accrediting bodies.

2.2 Release procedure of finished products

- detailed description of qualification requirements (education and work experience) of the authorized person(s)/qualified person(s) responsible for batch certification and releasing procedures;
- general description of batch certification and releasing procedure;
- role of authorized person/qualified person in quarantine and release of finished products and in assessment of compliance with the marketing authorization;
- the arrangements between authorized persons/qualified persons when several authorized persons/qualified persons are involved; and
- statement on whether the control strategy employs process analytical technology (PAT) and/or real-time release or parametric release.

2.3 Management of suppliers and contractors

- a brief summary of the establishment/knowledge of supply chain and the external audit programme;
- a brief description of the qualification system of contractors, manufacturers of APIs and other critical materials suppliers;
- measures taken to ensure that products manufactured are compliant with transmitting animal spongiform encephalopathy (TSE) guidance;²
- measures adopted where substandard/spurious/false-labelled/falsified/counterfeit medical products, bulk products (i.e. unpacked tablets), APIs or excipients are suspected or identified;
- use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;

² For further information please see: <http://www.who.int/bloodproducts/tse>.

- list of contract manufacturers and laboratories including the addresses and contact information and flowcharts of supply chains for outsourced manufacturing and QC activities, e.g. sterilization of primary packaging material for aseptic processes, testing of starting raw materials, etc., should be presented in Annex 4; and
- brief overview of the responsibility sharing between the contract giver and acceptor with respect to compliance with the marketing authorization (where not included under 2.2).

2.4 Quality risk management

- brief description of quality risk management (QRM) methodologies used by the manufacturer; and
- scope and focus of QRM including brief description of any activities which are performed at corporate level, and those which are performed locally. Any application of the QRM system to assess continuity of supply should be mentioned.

2.5 Product quality reviews

- brief description of methodologies used.

3. Personnel

- organization chart showing the arrangements for quality management, production and quality control positions/titles in Annex 5, including senior management and authorized person(s)/qualified person(s); and
- number of employees engaged in the quality management, production, quality control, storage and distribution, respectively.

4. Premises and equipment

4.1 Premises

- short description of plant: size of the site and list of buildings. If the production for different markets, i.e. for local country or regional economic areas, takes place in different buildings on the site, the buildings should be listed with destined markets identified (if not identified under 1.1);
- simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings are not required);
- layouts and flowcharts of the production areas (in Annex 6) showing the room classification and pressure differentials between adjoining areas and

indicating the production activities (i.e. compounding, filling, storage, packaging, etc.) in the rooms;

- layouts of warehouses and storage areas, with special areas for the storage and handling of highly toxic, hazardous and sensitizing materials indicated, if applicable; and
- brief description of specific storage conditions if applicable, but not indicated on the layouts.

4.1.1 Brief description of heating, ventilation and air-conditioning (HVAC) systems

- principles for defining the air supply, temperature, humidity, pressure differentials and air-change rates, policy of air recirculation (%).

4.1.2 Brief description of water systems

- quality references of water produced; and
- schematic drawings of the systems in Annex 7.

4.1.3 Brief description of other relevant utilities such as steam, compressed air, nitrogen, etc.

4.2 Equipment

4.2.1 Listing of major production and control laboratory equipment with critical pieces of equipment identified should be provided in Annex 8.

4.2.2 Cleaning and sanitation

- brief description of cleaning and sanitation methods of product contact surfaces (i.e. manual cleaning, automatic clean-in-place, etc.).

4.2.3 Good manufacturing practices critical computerized systems

- description of GMP critical computerized systems (excluding equipment-specific programmable logic controllers (PLCs)).

5. Documentation

- description of documentation system (i.e. electronic, manual); and
- when documents and records are stored or archived off-site (including pharmacovigilance data, when applicable): list of types of documents/records; name and address of storage site; and an estimate of time required to retrieve documents from the off-site archive.

6. Production

6.1 Type of products

References to Annex 1 or 2 can be made.

- type of products manufactured including:
 - list of dosage forms of both human and veterinary products which are manufactured on the site
 - list of dosage forms of investigational medicinal products (IMP) manufactured for any clinical trials on the site, and when different from the commercial manufacturing, information on production areas and personnel;
- toxic or hazardous substances handled (e.g. with high pharmacological activity and/or with sensitizing properties);
- product types manufactured in a dedicated facility or on a campaign basis, if applicable; and
- PAT applications, if applicable: general statement of the relevant technology; and associated computerized systems.

6.2 Process validation

- brief description of general policy for process validation; and
- policy for reprocessing or reworking.

6.3 Material management and warehousing

- arrangements for the handling of starting materials, packaging materials, bulk and finished products including sampling, quarantine, release and storage; and
- arrangements for the handling of rejected materials and products.

7. Quality control

- description of the QC activities carried out on the site in terms of physical, chemical and microbiological and biological testing.

8. Distribution, complaints, product defects and recalls

8.1 Distribution (to the part under the responsibility of the manufacturer)

- types (wholesale licence holders, manufacturing licence holders, etc.) and locations (countries or regional economic areas) of the companies to which the products are shipped from the site;
- description of the system used to verify that each customer/recipient is legally entitled to receive medicinal products from the manufacturer;
- brief description of the system to ensure appropriate environmental conditions during transit, e.g. temperature monitoring/control;
- arrangements for product distribution and methods by which product traceability is maintained; and
- measures taken to prevent manufacturers' products entering into the illegal supply chain.

8.2 Complaints, product defects and recalls

- brief description of the system for handling complaints, product defects and recalls.

9. Self-inspections

- short description of the self-inspection system with focus on criteria used for selection of the areas to be covered during planned inspections, practical arrangements and follow-up activities.

Annexes to a submission of a site master file

Annex 1 Copy of valid manufacturing authorization

Annex 2 List of dosage forms manufactured including the International Nonproprietary Names (INN) or common name (as available) of APIs used

Annex 3 Copy of valid GMP certificate

Annex 4 List of contract manufacturers and laboratories including the addresses and contact information, and flowcharts of the supply chains for these outsourced activities

Annex 5 Organizational charts

- Annex 6 Layouts of production areas including material and personnel flows, general flowcharts of manufacturing processes of each product type (dosage form)
- Annex 7 Schematic drawings of water systems
- Annex 8 List of major production and laboratory equipment

4.3 Guidelines for the preparation of a contract research organization master file

**Annex 7, WHO Technical Report Series, 957,
2010**

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Background

A contract research organization master file (CROMF) is a document prepared by the contract research organization (CRO) containing specific and factual information about the CRO and the conduct of clinical studies as well as the analyses of samples and related operations (including clinical trials, clinical data management, pharmacokinetics and statistical analysis and regulatory affairs) carried out at the named site. If only some of the operations referred to below are carried out at the site, the master file (MF) needs to be presented only for those operations.

In a case where a CRO is responsible for activities pertaining only to bioanalytical procedures, then only sections in the CROMF relating to these should be described. Other sections may be marked as “not applicable”.

Where a CRO performs various activities, separate sections could be prepared for the different units, e.g. clinical pharmacology unit (CPU) and bioanalytical laboratory (BAL).

A CROMF provides information on the policies, approach and general activities of a CRO. It is not trial-specific as trial-specific data are submitted in a product dossier. It serves as general information to regulators and can be used during preparation for inspections by regulatory inspectors in addition to the trial-specific data and information submitted for assessment. It also provides an overview of the organization’s approach to good clinical practices (GCP), good laboratory practices (GLP) and other guidelines pertaining to its activities.

A CROMF should be submitted to the national medicines regulatory authority (NMRA) where such a document is requested. It should be succinct and as far as possible not exceed 25 A4 pages (where appropriate, supportive documentation may be appended).

An updated CROMF should be submitted when requested by the NMRA, or if significant changes have been implemented by the CRO.

1. General information

- 1.1 Name and exact address of the CRO, including telephone, fax, 24-hour telephone numbers and e-mail address
- 1.2 Short description of the CRO (including size, location, number of beds, layout and plan, areas for handling samples and waste)
- 1.3 Activities as licensed/authorized by the national authority
- 1.4 Inspections and approvals
 - 1.4.1 Inspections/approvals/accreditations by any regulatory agency
 - 1.4.2 Audits of subcontractors

- 1.5 Type of studies (and indications, where appropriate) performed on site (a list of projects conducted at this site may be provided)
- 1.6 Provisions for insurance
 - 1.6.1 Number of employees engaged in studies, quality, storage and distribution
- 1.7 Contract services employed
 - 1.7.1 Use of outside scientific, analytical or other technical assistance in relation to studies and analysis (e.g. clinical laboratory, bioanalytical laboratory, X-ray facilities and caterers)
 - 1.7.2 Services outsourced, e.g. contracts with tertiary care hospital for handling of medical emergencies, ambulance facility, nutrition, biomedical waste, chemical waste, caterers, pest control and pathology laboratory

2. Quality management system of the contract research organization

(Short description including, e.g. responsibilities of the quality assurance unit. A list of quality system documents can be included)

- 2.1 Organization chart including the arrangements for quality assurance
- 2.2 Internal audits and self inspection
- 2.3 Corrective and preventive action plans (CAPA)

3. Personnel

(A brief description can be presented in tabular format)

- 3.1 Qualifications, experience and responsibilities of key personnel as applicable
 - 3.1.1 project manager
 - 3.1.2 principal investigator
 - 3.1.3 analytical investigator
 - 3.1.4 biostatistician
 - 3.1.5 clinical research associates
 - 3.1.6 data manager
 - 3.1.7 monitor
 - 3.1.8 the study director(s)
 - 3.1.9 person responsible for quality assurance

3.2 Training of personnel:

- 3.2.1 training policy and procedure (brief description)
- 3.2.2 training records

4. Ethics committee

- 4.1 Constitution and relation to CRO
- 4.2 Procedures including review and approval of protocols

5. Computer systems

(Short description)

- 5.1 Hardware
- 5.2 Software (and version number) used (e.g. in the bioanalytical laboratory, in pharmacokinetic and statistical analysis) and change control procedure
- 5.3 Data management systems (include a procedural flow chart and a brief description of query generation and resolution)
- 5.4. Security procedures
- 5.5 Electronic exchange of confidential information
- 5.6 Brief description of validation programme
- 5.7 Back-up and storage of electronic data

6. Equipment and instruments

- 6.1 Brief description of major equipment and instruments (a list of equipment is not required)
- 6.2 Qualification, maintenance and calibration programme, including the temperature recording systems

7. Documentation

- 7.1 Briefly describe document management systems
- 7.2 Project work flow including quality assurance and control process

- 7.3 Preparation of protocols
- 7.4 Preparation of informed consent forms and subject information forms
- 7.5 Preparation of report forms
- 7.6 Preparation of final report

8. Safety monitoring

(Brief description)

Adverse drug reaction reporting procedure

Provisions made for emergencies, including protocols and equipment available

9. Investigational medicinal products and comparator products

(Brief description)

- 9.1 Acquisition, storage, handling, sampling and disposal
- 9.2 Pharmacy and dispensing

10. Pathology

- 10.1 Biological sample collection and storage
- 10.2 Handling and analysis of biological samples

11. Bioanalytical laboratory

(Brief description)

- 11.1 Method development and validation
- 11.2 Reference standard materials used for preparation of calibration standards and quality control samples
- 11.3 Biological matrix storage, and handling of matrix samples
- 11.4 Analysis of unknown samples

11.5 Preparation and labelling of reagents

11.6 Storage of samples

11.7 Stability procedures

11.8 Waste management

12. Biostatistics

12.1 Data processing and analysis

12.2 Data management

13. Study volunteers

13.1 Procedure for recruitment

13.2 Collecting information on volunteers (e.g. databank), while confidentiality is maintained

13.3 Procedure for obtaining informed consent

14. Other information

14.1 Power supply system — uninterrupted power supply and generator availability and capacity

14.2 Brief description of any other activities performed on site by the CRO

14.3 Any other information which the CRO may feel it appropriate to add

4.4 WHO guidelines on technology transfer in pharmaceutical manufacturing

Annex 4, WHO Technical Report Series, 1044, 2022 (revised)

Background

During the fifty-fifth meeting of the World Health Organization Expert Committee on Specifications for Pharmaceutical Preparations, Expert Committee members were updated on the annual consultation on good practices for health products manufacture and inspection, which took place in July 2020 over a series of virtual meetings due to the COVID-19 pandemic. During these virtual meetings, a group of experts made a series of proposals for future activities, including a possible update of the *WHO guidelines on transfer of technology in pharmaceutical manufacturing* (1). This original document was published in 2011, since when numerous regulatory changes have been made. Transfer of technology is considered an integral part of the product life cycle management and is subject to regulatory expectations, including in the areas of a risk-based and science-based process and method design (such as a quality by design approach), achieving a state of control, and data governance. The original document therefore requires updating, not least to support the consistent supply of therapies for critical needs, including public health emergencies.

The Expert Committee asked the WHO Secretariat to explore this proposal.

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Abbreviations

ALCOA	attributable, legible, contemporaneous, original and accurate
API	active pharmaceutical ingredient
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
RU	receiving unit
SU	sending unit

1. Introduction

- 1.1 Technology transfer is a logical procedure involving the transfer of products, processes and knowledge, supported by relevant documentation and professional expertise. Technology transfer may include development, manufacturing and testing sites.
- 1.2 The transfer of production and control procedures of pharmaceutical products from one site to another may take place before or after obtaining regulatory marketing authorization. Product transfer may therefore occur during development, full-scale commercialization and commercial batch manufacturing. The level of rigour applied in the technology transfer should be commensurate with the respective product life cycle phase.
- 1.3 Technology transfer, particularly between different companies, has legal and economic implications that may include intellectual property rights, royalties, pricing, conflict of interest and confidentiality agreements. Such matters should therefore be addressed in undertaking the transfer.
- 1.4 Technology transfer requires a planned approach by trained, knowledgeable personnel working within a quality system with the appropriate documentation, data and information covering all aspects of development, production and quality control, as applicable, and considering the stage of the product life cycle and the regulatory requirements.
- 1.5 Technology transfer takes place between a sending unit (SU) and a receiving unit (RU). In some cases, it may be advantageous to establish a separate unit to manage the project.
- 1.6 The technology transfer project should fulfil the following general principles and requirements. There should be:

- a documented project plan covering the relevant aspects of the project;
 - a detailed quality risk management plan;
 - a comprehensive gap analysis, including due diligence performed covering technical, quality and regulatory aspects;
 - similar capabilities between the SU and RU, including facilities and equipment, where appropriate;
 - knowledge of the differences in process ability between the SU and RU, including the impact, risk and control strategies to overcome any differences;
 - a sufficient number of adequately trained personnel with suitable qualifications and experience;
 - effective process and product knowledge management;
 - effective communication and transparency between the SU and RU.
- 1.7 Technology transfer should include relevant documentation, data, information and knowledge from the SU in order to enable the RU to effectively execute the specified process or procedure in, for example, production and quality control. A successful technology transfer project should result in documented evidence that the RU can routinely reproduce the transferred product, process or procedure against a predefined set of specifications, as agreed between the SU and RU.
- 1.8 This document should be read in conjunction with other WHO guidelines, as referenced below (2–15), as well as other regulatory guidelines, including the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines Q7, Q8, Q9, Q10, Q11 and Q12. This guideline does not intend to replace any of those guidelines.
- 1.9 Product, process and procedure knowledge should be an essential part of the transfer process from the SU to the RU.
- 1.10 The critical quality attributes, critical process parameters, material attributes, control strategy and any other elements potentially impacting the quality of the product should be available (see also ICH guidelines).
- 1.11 This version of the document provides guiding principles reflecting current good practices in technology transfer and replaces the previous version published by the World Health Organization (WHO) (1).

2. Scope

- 2.1 This document provides guiding principles on technology transfer, including transfer from research and development to production sites, and between

two production sites. The principles therefore apply to newly commercialized products as well as to marketed products. The principles may also be applied to investigational products.

- 2.2 Throughout life cycle stages, transfers should be appropriate and proportionate to the phase of the product life cycle in order to ensure that product knowledge is maintained and that processes are appropriately controlled. This guideline should be applied when transferring the technology of manufacturing processes and analytical procedures relating to active pharmaceutical ingredients (APIs), isolated API intermediates, bulk drug products and finished pharmaceutical products. While medical devices as part of the finished pharmaceutical product of a combination medicinal product would be considered under this guidance, the specific regulatory and quality requirements for medical device manufacturing are covered under separate medical device regulations and quality management systems.
- 2.3 The guideline applies to all pharmaceutical dosage forms and may be adapted on a case-by-case basis by using risk management principles. Particular attention should be given to certain complex formulations, such as sterile products and metered dose inhalers.
- 2.4 Although this document focuses on pharmaceutical products, the principles can also be applied to the transfer of production, related processes and controls for other products, such as vaccines, biotherapeutic products, advanced therapy medicinal products, cell and gene therapy products, medical devices and vector control products.
- 2.5 Because each transfer project is unique, the provision of a comprehensive set of guidelines specific to a product or process is beyond the scope of this document.
- 2.6 This document does not provide guidance on any intellectual property, legal, financial or commercial considerations associated with technology transfer projects. These are prerequisites for a successful transfer that need to be defined and controlled prior to the transfer in the course of due diligence. Examples include health, safety and environmental aspects and the availability of confidentiality disclosure agreements, which should be in place prior to the start of the transfer.
- 2.7 This document addresses the following principal areas:
 - organization and management of the transfer;
 - transfer of relevant information in production, including processing, packaging and analytical procedures;
 - documentation, premises and equipment;

- personnel qualification and training;
- quality management and risk management;
- change management and life cycle approach;
- control strategy;
- qualification and validation.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They have been aligned as much as possible with the terminology in related WHO guidelines and good practices and included in the WHO *Quality Assurance of Medicines Terminology Database: list of terms and related guideline*,¹ but may have different meanings in other contexts.

acceptance criteria. Measurable terms under which a test result will be considered acceptable.

active pharmaceutical ingredient (API). Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

ALCOA+. A commonly used acronym for “attributable, legible, contemporaneous, original and accurate” that puts additional emphasis on the attributes of being complete, consistent, enduring and available – implicit basic ALCOA principles.

bracketing. An experimental design to test the extremes of, for example, dosage strength. The design assumes that the extremes will be representative of all the samples between the extremes.

change control. A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the registration and validated status. The intent is to determine the need for action that would ensure that the system is maintained in a regulatory compliant and validated state.

confirmation testing. An execution of tests that confirm and validate the results obtained by another test.

¹ https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/mqa-terminology-sept-2020.pdf?sfvrsn=48461fc_5.

control strategy. A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to API and finished pharmaceutical product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

corrective action. Any action to be taken when the results of monitoring at a critical control point indicate a loss of control.

critical. Having the potential to impact product quality or performance in a significant way.

critical process parameter. A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored and controlled to ensure the process produces the desired quality.

critical quality attribute. A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality.

design space. The multidimensional combination and interaction of input variables (such as material attributes) and process parameters that have been demonstrated to provide assurance of quality.

drug master file. Detailed information concerning a specific facility, process, packaging material or product submitted to the medicines regulatory authority, intended for incorporation into the application for marketing authorization.

finished pharmaceutical product. A product that has undergone all stages of production, including packaging in its final container and labelling. A finished pharmaceutical product may contain one or more APIs. In some cases, it may be in combination with a medical device.

gap analysis. The identification of the critical elements of a process that are available at the sending unit (SU) but are missing from the receiving unit (RU) with the objective of assessing which gaps have a potential impact on the process or method and to mitigate those gaps, as appropriate.

good manufacturing practices. That part of quality assurance that ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

good practices. A collection of quality guidelines and regulations in order to ensure that products are safe, effective, and of required quality; meet their intended use; and adhere to quality processes during production, control, storage and distribution.

in-process control. Checks performed during production in order to monitor and, if necessary, adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

installation qualification. Documented verification that the installations (such as machines, equipment and instruments, computer system components, measuring devices, utilities and manufacturing) used in a processor system are appropriately selected and correctly installed, in accordance with established specifications.

intercompany transfer. A transfer of technology between the sites of different companies.

intracompany transfer. A transfer of technology between sites of the same group of companies.

marketing authorization holder. An individual or a corporate entity being in possession of a marketing authorization of a pharmaceutical product.

operational qualification. Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.

process validation. The collection and evaluation of data, from the process design stage through to commercial production, that establish scientific evidence that a process is capable of consistently delivering the API or finished pharmaceutical product meeting its predetermined specifications and quality attributes.

qualification. Documented evidence that premises, systems or equipment are able to achieve the predetermined specifications when properly installed and working correctly, and lead to the expected results.

quality assurance. Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the objective of ensuring that pharmaceutical products are of the quality required for their intended use.

quality control. All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that starting materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

quality planning. Part of quality management, quality planning entails setting quality objectives and specifying necessary operational processes and related resources to fulfil the quality objectives.

quality policy. A brief statement that describes the organization's purpose, overall intentions and strategic direction; provides a framework for quality objectives; and includes a commitment to meet applicable requirements.

quality risk management. A systematic process for the assessment, control, communication and review of risks to the quality of the pharmaceutical product throughout the product's life cycle.

receiving unit (RU). The involved disciplines at an organization where a designated product, process or method is expected to be transferred.

sending unit (SU). The involved disciplines at an organization from where a designated product, process or method is expected to be transferred.

standard operating procedure. An authorized written procedure giving instructions for performing operations, not necessarily specific to a given product or material, but of a more general nature (for example, operation of equipment, maintenance and cleaning, validation, cleaning of premises, and environmental control, sampling and inspection). Certain standard operating procedures may be used to supplement product-specific master and batch production documentation.

starting material. Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

technology transfer, transfer of technology. A logical procedure that controls the transfer of any product or process, including product or process knowledge, together with its documentation and professional expertise. Technology transfer may involve development, manufacturing or testing sites.

technology transfer protocol (master plan). A document that describes the intended sequential phases and activities of the transfer, and serves as a plan for the execution and management of the transfer.

technology transfer report. A documented summary of a specific technology transfer project listing procedures, acceptance criteria, results achieved and conclusions.

validation. Action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.

validation batches. Those batches produced by the receiving unit (RU) to demonstrate its ability to manufacture the transferred product in compliance with its predetermined specifications, or as part of process performance qualification.

validation master plan. A high-level document that summarizes the manufacturer's overall philosophy and approach, to be used for establishing performance adequacy.

It provides information on the manufacturer's qualification and validation work programme and defines details of and timelines for the work to be performed, including a statement of the responsibilities of those implementing the plan.

validation protocol. A document describing the activities to be performed during validation, including the acceptance criteria.

validation report. A document in which the records, results and evaluation of validation are documented and summarized. It should also contain a conclusion of the outcome of the validation.

4. Due diligence and gap analysis

- 4.1 When considering a technology transfer project, the first steps should include a process of due diligence and gap analysis through visits to the SU and RU.
- 4.2 The suitability and degree of preparedness of the RU should be assessed prior to the start of the transfer. The procedure to be followed and the results and conclusions should thereafter be documented.
- 4.3 The gap analysis should be performed by a team of appropriately qualified persons with knowledge and experience in the field of good practices and the activity to be transferred. It is recommended that the quality units of the SU and RU participate in this activity. The team should be involved throughout each phase of the project, as appropriate (see section 12 on phases of a technology transfer project).
- 4.4 The gap analysis should further cover the capabilities and resources related to personnel, premises, equipment and instruments, utilities, cleaning, quality control, documentation, computerized systems, qualification, validation, and further health, safety and environment-related considerations, including waste management.
- 4.5 The gap analysis to determine the feasibility for technology transfer may include technical, engineering, business, quality, regulatory, supply and legal aspects.

5. Organization and management

- 5.1 All technology transfer activities should be organized and planned.
- 5.2 There should be formal written agreements, signed between the parties involved in technology transfer, that specify the responsibilities of each party before, during and after transfer. The agreements should cover, for example, data management, data integrity, documentation and validation.

- 5.3 All the necessary activities to be executed during the technology transfer project should be identified, organized and documented at the start of the project. The responsibilities of the SU, RU, sponsor and marketing authorization holder should be defined in writing.
- 5.4 Where applicable, the marketing authorization holder should coordinate the transfer of the necessary documentation related to the technology transfer from the SU to the RU, including the relevant regulatory documents. The product dossier, production and control documentation should be assessed for compliance with regulatory requirements before the transfer of the documentation.
- 5.5 The SU should provide criteria and information on the inherent risks, hazards and critical steps associated with the process, product or procedure to be transferred. These may serve as a basis for the gap analysis and risk assessment exercises.
- 5.6 The technology transfer should be managed by responsible persons from each site (the SU and RU) and any other units with the appropriate technical and quality oversight. A technology transfer team may be appointed with identified and documented responsibilities.
- 5.7 The team members should have the necessary qualifications and experience to manage the particular aspects of the transfer.
- 5.8 The SU should make available in relevant documents all the necessary information and knowledge with regard to the product, process or procedure in order to ensure a successful transfer.
- 5.9 The RU should be able to accommodate the intended production capacity. If possible, it should be established at the outset whether or not the intention is to perform single-batch manufacture, continuous production or campaigns.
- 5.10 Consideration should be given to the level and depth of detail to be transferred to support production and any further process development and optimization at the RU, as intended under the transfer project plan.
- 5.11 Consideration should be given to the technical expertise, site technology and site capabilities of the RU. Any product and process robustness issues should be identified at the outset by the SU so that plans may be put in place at the RU.
- 5.12 The SU should assess the suitability and degree of preparedness of the RU before transfer with regard to personnel, premises, equipment, materials, suppliers and support services (specifically, purchasing and inventory control mechanisms and the pharmaceutical quality system – quality control procedures, documentation, computer validation, site validation, equipment qualification, water for pharmaceutical production and waste management).

- 5.13 The SU and the RU should jointly verify that the following, satisfactorily completed, qualification and validation protocols and reports are available:
- installation qualification and operational qualification data for manufacturing and packaging equipment at the RU site and analytical equipment;
 - qualification of the rooms for both manufacture and packaging at the RU site;
 - cleaning validation.
- 5.14 A training programme should be implemented covering various topics, including those specific to the process, product or procedure to be transferred. The effectiveness of training should be evaluated. Records should be maintained.
- 5.15 Changes and adaptations made during the course of the project should be done in accordance with a standard procedure. Risk assessment, where appropriate, should cover technical, quality, regulatory and other aspects. The project manager should evaluate the impact to the project cost, schedule, and resourcing based on an updated risk assessment.
- 5.16 The execution of the technology transfer project should be documented, for example in a report, supported by the relevant data. The overall technology transfer strategy and acceptance criteria to confirm a successful transfer should be documented a priori in the technology transfer protocol. These should consider the stage of development – both clinical and commercial stages (including the fulfilment of relevant regulatory country requirements).
- 5.17 Whenever possible, targeted on-site or virtual visits between the SU and RU at critical phases of the project should be allowed to assist with the transfer of knowledge.
- 5.18 Data should be in accordance with ALCOA+ principles.

6. Quality management and quality risk management

- 6.1 The SU and RU should each have an appropriately designed, clearly defined and documented quality management system.
- 6.2 The quality management system should be adequately resourced, implemented and maintained.
- 6.3 The quality management system should incorporate good practices that should be applied to the life cycle stages of the products and processes, including technology transfers.

6.4 The quality management system should ensure that:

- responsibilities are clearly specified in writing
- operations are clearly defined in writing
- there is a system for change management
- there is a system for quality risk management
- arrangements are made for the documented technology transfer.

6.5 Quality risk management should be implemented as a systematic process for the assessment, control, communication and review of risks.

6.6 The system for quality risk management should be described in writing and cover appropriate areas, including premises, equipment, materials, products, production, processes, quality control and microbiology, qualification, validation and the process of technology transfer.

6.7 The evaluation of the risk should be based on scientific knowledge and experience, including that of the process and product.

6.8 The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

6.9 The procedures and records for quality risk management should be retained.

7. Documentation

7.1 An authorized technology transfer document – for example, a master plan or technology transfer protocol – should list the intended sequential phases and activities of the transfer, where appropriate. The document should include the following:

- title;
- objective;
- scope;
- names and addresses of the SU and RU;
- technology transfer team, including key personnel and their responsibilities, from SU and RU;
- phases of the project, including key activities, deliverables and associated accountabilities;
- approximate timing of key activities and deliverables, including the timing of trial production batches and validation batches;

- reference to other transfer plan documents relevant to the process being transferred;
- reference to validation master plans relevant to the process being transferred, including equipment, facilities and utilities qualification project plan, site-independent or site-dependent process validation master plan, method validation master plan;
- reference to gap analysis and risk assessments;
- acceptance criteria for a successful transfer;
- a parallel comparison of premises, equipment, instruments, materials, procedures, and methods for the transfer under consideration.

Note: A list with examples of documents commonly required in technology transfer is presented in Appendix 1.

- 7.2 Standard operating procedures should be followed, describing the actions to be taken during the technology transfer process.
- 7.3 Records should be maintained of the activities performed during the technology transfer process (such as a technology transfer report). The report content should reflect the protocol and standard operating procedures that were followed. The report should summarize the scope of the transfer, the critical parameters as obtained in the SU and RU, and the final conclusions of the transfer. Changes, deviations, investigations and the relevant appropriate actions taken should be recorded. The SU should provide all the relevant supportive documents with data, results and other relevant information in order to facilitate a successful technology transfer.

8. Premises

- 8.1 The RU should have appropriate premises with a layout, construction and finishing suitable for the intended operations. Utilities such as heating, ventilation and air-conditioning, as well as gas and water systems, should have sufficient capacity and should be appropriate for the intended process, product or procedure to be transferred.
- 8.2 The SU should provide the RU with information on relevant health, safety and environmental issues, including:
 - the inherent risks of the manufacturing processes (for example, reactive chemical hazards, exposure limits, fire and explosion risks, microbiological contamination risks);
 - health and safety requirements to minimize operator exposure to and ensure containment and management of pharmaceutical waste;

- emergency planning considerations (for example, in case of gas or dust release, spillage, fire or firewater run-off);
- identification of waste streams and provisions for reuse, recycling or disposal, including antimicrobial substances.

9. Equipment and instruments

- 9.1 The SU should provide a list (or similar document) of equipment and instruments involved in production, filling, packing, quality control and microbiological testing. It should include the makes and models of the relevant equipment and instruments, including automated systems and those of single use, in order to ensure the evaluation of similar principles of operation.
- 9.2 A review and side-by-side comparison of the equipment and instruments, as well as process steps and parameters of the SU and RU, should be carried out in terms of their working principle, capacity, make and model to ensure that they are capable of appropriately performing the required processes and methods.
- 9.3 The facility- and building-specific location of all equipment at the RU should be considered at the time of drawing up process maps or flowcharts of the manufacturing process to be transferred, including the flow of personnel and the flow and intermediate storage of materials.
- 9.4 Where the review and comparison identify any gaps or differences, the appropriate action should be taken. This may include the adaptation of existing equipment or the acquisition of new equipment. Any modification or adaptation of existing equipment to become capable of reproducing the process being transferred should be documented.
- 9.5 Production volumes and batch sizes at the SU and RU should be compared. Where batch sizes are different, the impact should be assessed as part of risk assessment and the appropriate action planned and taken. Other factors relating to equipment to be reviewed may include:
 - minimum and maximum capacity
 - material of construction of contact surfaces
 - critical operating parameters
 - components (such as filters, screens, and temperature or pressure sensors)
 - range of intended use.
- 9.6 The impact of the potential product to be transferred on existing products manufactured on site (and vice versa) should be assessed.

10. Qualification and validation

- 10.1 The extent of qualification and validation to be performed should be determined on the basis of risk management principles, taking into account the product's life cycle phase.
- 10.2 Equipment and instruments should be qualified and calibrated before using them to support the technology transfer activities.
- 10.3 Process validation should be done according to guidelines, as published in the WHO Technical Report Series (3).
- 10.4 Production processes and analytical procedures should be appropriately transferred to the RU following documented procedures. Where validation data exist, these should be included in the transfer.
- 10.5 For cleaning procedures, development and validation should be done in accordance with the guidelines published in the WHO Technical Report Series (6). Points to consider when including health-based exposure limits in cleaning validation (14) should be taken into account in establishing cleaning procedures, undertaking cleanability studies and setting acceptance limits.
- 10.6 Analytical procedures should be validated or verified according to the guidelines published in the WHO Technical Report Series (7).
- 10.7 Qualification and validation procedures, protocols, data and results should be appropriately recorded. The documents should be retained as defined in procedures.

11. Life cycle approach

- 11.1 The relevant stage of the life cycle of the facility, equipment, instrument, utility, product, process or procedure to be transferred should be taken into consideration when the transfer is planned and executed. This also applies to the control strategy and process validation.
- 11.2 The responsible entities should monitor the progress of the project at each applicable stage of the life cycle aspect of the transfer to ensure successful completion of the transfer.

12. Phases of a technology transfer project

- 12.1 The technology transfer project plan may be divided into different phases. These may include:

- Phase I: Project initiation
- Phase II: Project planning
- Phase III: Project transfer execution
- Phase IV: Project review and closeout.

Phase I: Project initiation

- 12.2 During the initiation phase of the project, a unit normally identifies the need for the technology transfer. This may be due to a lack of capacity, a transfer from development to commercial site or a transfer from one company to another.
- 12.3 During an initial discussion, it should be identified whether or not an RU has any interest in such a project (see also the section on due diligence above).
- 12.4 The RU should be able to accommodate the intended activity.
- 12.5 The RU should have the necessary technical expertise, technology and capability.
- 12.6 A sufficient level and depth of detail to support the activity, and any further development and optimization at the RU, should be transferred.

Phase II: Project planning

- 12.7 The marketing authorization holder, SU and RU should jointly establish a team that will coordinate activities and execute the technology transfer exercise. Where the technology transfer involves a site that has limited manufacturing experience or the process being transferred is complex, the SU should consider providing extensive training and on-site support before the project execution phase begins.
- 12.8 The team should perform a gap analysis and risk assessment based on the available data, information and knowledge of the premises, equipment, materials, products, procedures and other related information.
- 12.9 The team should prepare the technology transfer document, such as the master plan or technology transfer protocol.
- 12.10 The team should develop a control strategy that includes:
- risks
 - raw, starting and packaging material attributes
 - analytical and microbiological test procedures
 - sampling plans and release and stability specifications
 - critical quality attributes, critical process parameters and in-process controls
 - acceptance criteria and limits.

- 12.11 The specifications and critical material attributes of the starting materials (APIs and excipients) to be used at the RU should be consistent with those materials used at the SU unless there is a planned change associated with these materials as part of the transfer and regulatory approval is obtained, as applicable. Documentation to support compliance with transmissible animal spongiform encephalopathy certification requirements, or other regulatory requirements, should be present at the RU, where applicable.
- 12.12 The SU should provide the RU with the open part of the drug master file or API master file, as applicable, or equivalent information, as well as any relevant additional information on the API of importance to the manufacture of the pharmaceutical product.
- 12.13 The SU should provide to the RU product information, including its qualitative and quantitative composition, physical description, method of manufacture, in-process controls, control method and specifications, packaging components and configurations, and any safety and handling considerations.
- 12.14 The marketing authorization holder or SU should provide any information on the history of process development as well as any historical process changes that may be required to enable the RU to perform any further development or process optimization after successful transfer.
- 12.15 The SU should provide to the RU information on any health, safety and environmental issues associated with the manufacturing processes to be transferred and the implications thereof (for example, need for gowning or protective clothing).
- 12.16 The SU should provide to the RU information on current processing and testing, including:
 - a detailed description of facility requirements and equipment;
 - information on starting materials, applicable material safety data sheet where required, and storage and distribution requirements for raw materials, intermediates and finished products;
 - description of manufacturing steps (narrative and process maps or flowcharts and master batch records), including the qualification of in-processing hold times and conditions, and the order and method of raw material addition and bulk transfers between processing steps;
 - description of analytical procedures;
 - identification and justification of control strategy (for example, identification of critical performance aspects for specific dosage forms,

- identification of process control points, product quality attributes and qualification of critical processing parameter ranges, sampling plans, and statistical process control charts);
 - design space, in cases where this has been defined;
 - validation information (such as validation plans and reports);
 - annual product quality reviews;
 - stability information;
 - an authorized set of protocols and work instructions for manufacturing;
 - environmental conditions or any special requirement needed for the facility or equipment, depending on the nature of the product to be transferred.
- 12.17 Information on packaging to be transferred from the SU to the RU should include specifications for a suitable container and closure system, as well as any relevant additional information on design, packing, processing or labelling requirements and tamper-evident and anticounterfeit measures.
- 12.18 For quality control and microbiological testing of packaging components, specifications should be provided, including drawings, artwork and material and reference to relevant pharmacopoeias, where applicable.

Phase III: Project transfer execution

- 12.19 The team should execute the project in accordance with the procedures and agreed plan.

Production (example: finished pharmaceutical product)

- 12.20 During the transfer process, the RU should identify any differences in facilities, systems and capabilities and discuss these with the SU. The SU should cooperate with the RU to understand the potential impact and satisfactorily address this in order to assure equivalent product quality. Based on the information received from the SU, the RU should consider its own capability to manufacture and pack the product to the required standards and should develop the relevant site operating procedures and documentation before the start of routine production.

- 12.21 The RU should address the following tasks:

- comparison and assessment of suitability and qualification of facility and equipment;
- description of manufacturing process and flow of personnel and of materials at the RU (narrative or process maps or flowcharts);

- determination of critical steps in manufacture, including hold times, end-points, sampling points and sampling techniques;
- writing and approval of a training plan and standard operating procedures for all production operations (for example, dispensing, granulation or blending or solution preparation, tablet compression, tablet coating, encapsulation, liquid filling, primary and secondary packaging and in-process quality control and microbiology), packaging, cleaning, testing and storage;
- evaluation of stability information, with generation of site-specific stability data if required;
- compliance with regulatory requirements for any changes made that may impact the quality and efficacy of the product.

12.22 The transfer of packaging operations should follow the same procedural principles as those of the product processing.

12.23 The RU should determine the need for qualification and validation for the packaging process.

Quality control: analytical procedure transfer

12.24 Analytical procedures used to test pharmaceutical products, starting materials, packaging components and cleaning (residue) samples, if applicable, should be implemented at the testing laboratory before the testing of samples for process validation studies is performed by the RU. The transfer of the analytical procedure may be accomplished by several approaches, such as confirmation testing, comparability testing between SU and RU results, co-validation between laboratories, or through paper-based knowledge transfer. The strategy chosen should be risk based and scientifically justifiable.

12.25 A protocol and test transfer plan defining the steps should be prepared for the transfer of analytical procedures. The analytical procedures transfer protocol should include:

- a description of the objective, scope and responsibilities of the SU and the RU;
- a specification of materials and methods;
- the experimental design and acceptance criteria;
- documentation (including information to be supplied with the results and report forms to be used, if any);
- procedure for the handling of deviations;
- details of test samples (starting materials, intermediates and finished products).

12.26 The SU's responsibilities for the transfer of analytical procedures typically are to:

- provide method-specific training for analysts and other quality control and microbiology staff, if required;
- assist in analysis of quality control and microbiology testing results;
- define all procedures to be transferred for testing a given product, starting material or cleaning sample;
- define experimental design, sampling methods and acceptance criteria;
- provide any validation reports for procedures under transfer, including proof of their robustness;
- provide details of the equipment used, as necessary (part of the validation report, if available) and any standard test samples;
- provide approved procedures used in testing;
- review and approve transfer reports.

12.27 The RU should exercise its responsibility to:

- review analytical procedures provided by the SU, and formally agree on acceptance criteria before execution of the transfer protocol;
- ensure that the necessary equipment for quality control is available and qualified at the RU site, and that the equipment used by the RU during the analytical transfer meets the appropriate specifications in order to ensure the requirements of the procedure or specification are met;
- ensure that adequately trained and experienced personnel are in place for analytical testing;
- provide a documentation system capable of recording receipt and testing of samples to the required specification using approved test procedures, and of reporting, recording and collating data and designation of status (approved, rejected, quarantine);
- execute the transfer protocol;
- perform the appropriate level of validation or verification to support the implementation of the procedures;
- generate and obtain approval of transfer reports.

12.28 The appropriate training should be provided and all training activities and outcomes should be documented.

12.29 Reference should be made to recognized compendial monographs, where these are relevant.

12.30 An experimental design should be prepared that includes acceptance criteria for the analytical testing procedures.

- 12.31 Where products are transferred from one unit to another, the applicable analytical procedures should also be transferred.
- 12.32 Relevant analytical procedure development and validation documentation should be made available by the SU to the RU, if required.
- 12.33 The appropriate transfer protocols and procedures should be followed when analytical procedures are transferred.
- 12.34 The number of analysts involved in the transfer, from both SU and RU, should be defined and justified.
- 12.35 The parameters to be included in the experimental evaluation of the transfer of the analytical procedure should be defined and justified.
- 12.36 Acceptance criteria should be set to determine the success of the transfer and capability of the process and procedures; where appropriate, statistical trending of results should be undertaken in order to demonstrate this.

Cleaning

- 12.37 To minimize the risk of contamination and cross-contamination, adequate cleaning procedures should be followed.
- 12.38 Cleaning procedures and their validation should normally be site specific. In order for the RU to define its cleaning strategy, the SU should provide information on cleaning at the SU to minimize cross-contamination due to residues from previous manufacturing steps, operator exposure and environmental impact, including:
 - information on cleanability;
 - information on solubility of active ingredients, excipients and vehicles;
 - toxicological assessment, including health-based exposure limits;
 - existing cleaning procedures.
- 12.39 Additional applicable information should be provided, such as:
 - cleaning validation reports (chemical and microbiological);
 - potential degradation products and impurities;
 - risks of antimicrobial resistance;
 - information on cleaning agents used (efficacy, evidence that they do not interfere with analytical testing for residues of APIs, removal of residual cleaning agents);
 - recovery studies to validate the sampling methodology.

- 12.40 Before the transfer, the SU should provide information on limits for product residues and the rationale for limit selection.
- 12.41 Based on the information provided by the SU, cleaning procedures should be designed at the RU, considering relevant characteristics of the residues to be cleaned (such as potency, toxicity and solubility), manufacturing equipment design and configuration, and cleaning agent.

Phase IV: Project review and close-out

- 12.42 The progress and success of the technology transfer should be monitored and reviewed during and after completion of the project. The review should further ensure that, as appropriate, stability studies are started and continued; post-marketing commitments are monitored; and new material suppliers are integrated into the quality management system.
- 12.43 Compliance with the procedures and protocols should be verified. Deviations and changes should be documented and investigated, where appropriate.
- 12.44 Where possible, data and results should be subjected to appropriate statistical calculation and evaluation to determine trends and compliance with control limits and capability studies.
- 12.45 A document such as a technology transfer report should be prepared, based on the data and information obtained during the project. The supportive data should be stored and should be accessible.
- 12.46 The document, which should include an assessment of the data and information and a conclusion, should be authorized by the appropriate responsible person or persons. It should further state whether or not the team has achieved the completion of the technical transfer. Any deviations and changes from the master plan should additionally be assessed and evaluated before close-out of the project.

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Appendix 1

Documentation commonly required for technology transfer

Table 1 provides examples of the documentation commonly required for technology transfer. Note that these are examples: all the required documents should be identified for the different tasks.

Table 1
Documentation commonly required for technology transfer

Aspect	Related documentation
Regulatory	Regulatory process description Applicable regulatory documentation
Starting materials (active pharmaceutical ingredients (APIs) and excipients)	Drug master file, API master file, active substance master file Material safety data sheets Product development report Storage conditions Stability data Forced stability data Specifications Supplier qualification References
Formulation	Formulation development reports Master formula Material compatibility and interaction studies Specifications for delivery devices
Batch manufacturing	Master of executed batch record Scale-up information Risk assessment Critical process parameters In-process control specification Scale-up protocol and report Process validation

Table 1 *continued*

Aspect	Related documentation
Packaging	Packaging material specification Master of executed packaging record Validation Sampling plan Acceptance quality level for products and defects Packaging validation
Finished product	Specification Product dossier
Analytical procedures	Analytical test procedures Analytical procedure development Analytical procedure validation Standard test procedures Instrument specifications
Quality control	Sampling procedures (e.g. in-process control) Stability testing protocol and procedures Release test analytical procedure validation
Equipment and instruments	List of equipment and instruments Preventive maintenance information Overview of qualification
Cleaning	Cleaning validation master plan Cleaning procedure development and cleanability Cleaning procedures Health-based exposure level (permitted daily exposure) information reports Analytical procedures validation for cleaning Cleaning validation reports and recovery study reports
Other documents	Recalls and complaint reports Bio-batch information Pilot batch information History of changes and change management Hold time protocols and reports

4.5 WHO guidelines on quality risk management

Annex 2, WHO Technical Report Series, 981,
2013

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1. Introduction

1.1 Background and scope

In most countries compliance with good manufacturing practices (GMP) (1, 2) (including validation), medicines regulatory activities and inspections, together with supply chain controls throughout the product life-cycle, provide good assurance that risks are largely controlled. However, where control is less effective, patients may be put at risk through the production of medicines of inadequate quality. The assessment of individual risks related to specific products and starting materials and the recognition of hazards at specific stages of production or distribution should permit regulatory authorities to improve control of medicines by increasing the effectiveness of their activities within the limits of the available resources. Quality risk management (QRM) is a process that is relevant to all countries and should provide a rationale to understand risk and mitigate it through appropriate and robust controls.

The aim of these guidelines is to assist the development and implementation of effective QRM, covering activities such as research and development, sourcing of materials, manufacturing, packaging, testing, storage and distribution. In the past, hazard analysis and critical control point (HACCP) methodology, traditionally a food safety management system but subsequently applied to other industries, has been the basis of WHO risk management guidance to the pharmaceutical industry (3).

More recently international guidance has emerged (2, 4–7) that is of specific relevance to the pharmaceutical industry and which addresses the full scope of pharmaceutical industry QRM more effectively than HACCP principles, including how to structure regulatory filings using a risk-based approach. Consequently, these WHO guidelines have been developed as an update on WHO's advice to the pharmaceutical industry, taking account of this new guidance.

To protect patients in terms of quality, safety and efficacy of medicines, international medicines regulatory authorities (MRAs) are recommending pharmaceutical manufacturers to adopt a risk-based approach to the life-cycle of a pharmaceutical product. Some MRAs require the adoption of a risk-based approach for specific areas in the life-cycle of a pharmaceutical product, e.g. environmental monitoring in sterile products manufacture. The level of QRM activity and the density of associated documentation will evolve as the product progresses from early development through to routine production.

QRM is the overall and continuing process of appropriately managing risks to product quality throughout the product's life-cycle in order to optimize its benefit–risk balance. It is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

While the choice of the tools to support the QRM approach is optional and may vary, the tools chosen need to be appropriate for the intended use.

In return for using this approach, there are potential opportunities for both MRAs and pharmaceutical manufacturers (8) as summarized in the following sections.

- Quality risk management (QRM) principles can be applied to both MRAs and pharmaceutical manufacturers:
 - MRAs: systematic and structured planning of reviews and inspections that are risk-based. The submission review and inspection programmes can also operate in a coordinated and synergistic manner.
 - Manufacturers: design, development, manufacture and distribution, i.e. the life-cycle of a pharmaceutical product. QRM should be an integral element of the pharmaceutical quality system (QS).
- Science-based decision-making can be embedded into QRM processes:
 - MRAs: decisions regarding review, inspection or inspection frequency should consider product risk and GMP compliance of the manufacturer. The MRA accepts residual risks through understanding the QRM decisions involved.
 - Manufacturers: quality decisions and filing commitments can be based on a science-based understanding of the process and QRM (when using the quality by design approach, and other approaches where appropriate). Its effective application should offer manufacturers greater freedom to decide how to comply with the principles of GMP and this, therefore, should encourage innovation.

The control strategy for the process focuses on critical quality attributes and critical process parameters.

- Resources can be focused on risks to patients:
 - MRAs: QRM can be used to determine the best allocation of inspection resources, both in terms of product types and for specific areas of focus for a given inspection. This enables the most efficient and effective scrutiny of the most significant health risks. Those manufacturers with poor histories of GMP compliance can also be more closely and frequently evaluated by on-site inspection than those manufacturers with better records.
 - Manufacturers: evaluation of quality risk through science-based decisions can be linked ultimately to protection of the patient by ensuring the quality, safety and efficacy of the product. A corporate culture is supported to produce cost-effective medicines, without

compromising quality, while maintaining the focus on the patient as a primary stakeholder in all activities.

- Restrictive and unnecessary practices can be avoided:
 - MRAs: regulatory scrutiny should consider the level of risk to patients. Improvement and innovation by manufacturers should be encouraged.
 - Manufacturers: instead of having systems designed to inhibit change and minimize business risk, changes can be managed within a company's quality management system. Innovation and the adoption of the latest scientific advances in manufacturing and technology are supported. Unnecessary testing can be eliminated, for example, with real-time release testing.
- Communication and transparency are facilitated:
 - MRAs: facilitate dialogue with pharmaceutical manufacturers and communicate clearly to the industry and the public how the inspection programme may be adjusted based on the risk to patients. Information-sharing between MRAs will contribute to a better risk management approach globally.
 - Manufacturers: matrix team approach, stakeholders are kept informed through science-based decisions. This builds a culture of trust and a “one-team” mindset with a focus on the product and the patient.

These guidelines will align with the general framework described in other current international guidance on this subject.

1.2 Principles of quality risk management

It is not always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures, e.g. standard operating procedures (SOPs)). The use of an informal risk management process (using empirical tools or internal procedures) can also be considered acceptable.

The two primary principles of QRM are that:

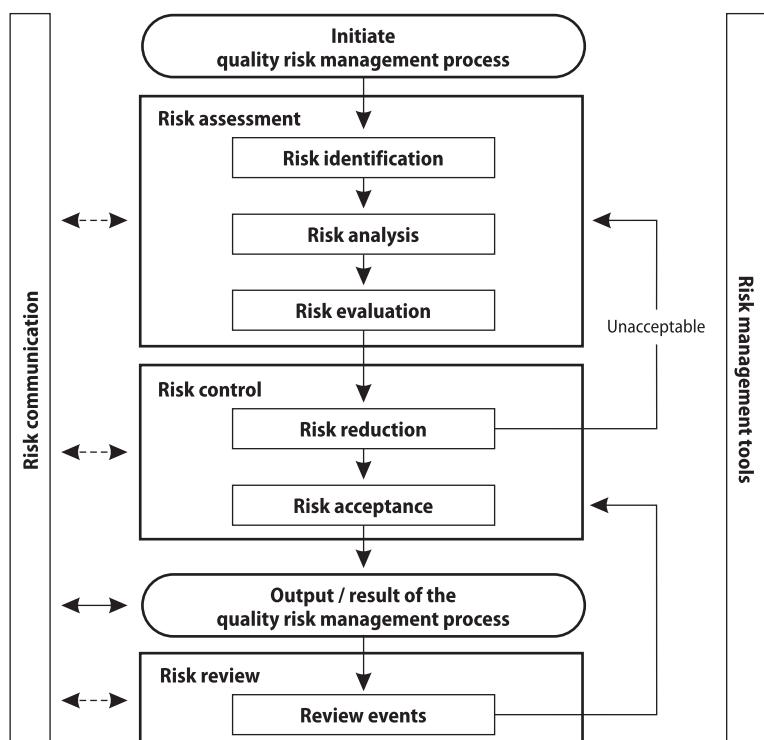
- The evaluation of the risk to quality should be based on scientific knowledge and ultimately linked to the protection of the patient.
- The level of effort, formality and documentation of the QRM process should be commensurate with the level of risk.

In addition to the two principles above, the following principles are also part of the QRM methodology:

- When applied, processes using QRM methodologies should be dynamic, iterative and responsive to change.
- The capability for continual improvement should be embedded in the QRM process.

This guidance describes the WHO approach to QRM, using the concepts described in ICH Q9 (6) and illustrated in Figure A3.1. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Figure A3.1
Overview of a typical quality risk management process



Reproduced from reference 5: ICH Q9: Quality Risk Management.

Decision points are not shown in the diagram above because decisions can occur at any point in the process. The decision might be:

- to return to the previous step and seek further information;
- to adjust the risk models; or even
- to terminate the risk management process based upon information that supports such a decision.

The approach described in these guidelines may be used to:

- systematically analyse products and processes to ensure that the best scientific rationale is in place to improve the probability of success;
- identify important knowledge gaps associated with processes that need to be understood to properly identify risks;
- provide the communication process that will best interface with all relevant parties involved in the QRM activities;
- facilitate the transfer of process knowledge and product development history to ease product progression throughout its life-cycle and to supplement already available knowledge about the product;
- enable the pharmaceutical industry to adopt a risk-based approach to development as described in regulatory guidance (4–6). The QRM outputs will potentially serve as reference documents to support product development and control strategy discussions in regulatory filings.

Early in development, the purpose of the QRM process may be to acquire sufficient product and process knowledge to assess risks associated with formulation development of the finished pharmaceutical product (FPP) according to the quality target product profile (QTPP). In recognizing risks and knowledge gaps, the QRM process plays a significant role in proactively enabling the prioritization and mitigation of risks. The objective is to develop the FPP through maximizing product and process knowledge and risk mitigation.

As FPP development progresses, in addition to supporting that development, the purpose of the QRM process is to determine and manage risks to bioavailability, safety, efficacy and product quality. QRM in development should differentiate process parameters and quality attributes from critical process parameters (CPPs) and critical quality attributes (CQAs), thereby contributing to defining and refining the control strategy.

The long process of product development is inevitably complex and requires the continual exchange of data, decisions and updates both internally within companies and, where required, with external stakeholders, such as MRAs. A crucial aspect of product development and QRM is the maintenance of an effective and secure knowledge

management and documentation system. Such a system must facilitate transparent communication and the highlighting of key issues to stakeholders and must also include a well-structured archive. Clearly, the ability to organize diverse data and information effectively and then retrieve it as required for updating and further evaluation, e.g. for the purposes of process validation, would be hugely beneficial.

Finally, it should be noted that QRM activities are focused on the product/process development and product manufacturing, ultimately to ensure a robust, safe and effective FPP.

2. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

control strategy

A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active pharmaceutical ingredients (APIs) and finished pharmaceutical product (FPP) materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

critical quality attribute (CQA)

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

failure mode

Different ways that a process or subprocess can fail to provide the anticipated result.

failure mode, effects and criticality analysis (FMEA)

A systematic method of identifying and preventing product and process problems.

finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

formal experimental design

A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as “design of experiments”.

occurrence

Probability of negative events within a fixed time frame.

pharmaceutical product

Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

pharmaceutical product target profile (PPTP)

A definition of the target properties of the FPP, including dosage form and strength(s), route of administration and relevant drug release and pharmacokinetic requirements.

planned risk assessment

An assessment that is conducted in advance of an activity, either before any work is conducted or before further work is conducted. This enables quality to be built into activities and risk to be reduced, e.g. design of high containment facilities for manufacture of cytotoxic products.

process robustness

Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

qualification

The action of proving and documenting that any premises, systems and equipment are properly installed and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation.

quality critical process parameter

A process parameter which could have an impact on the critical quality attribute.

quality risk management

A systematic process for the assessment, control communication, and review of risks to the quality of the pharmaceutical product across the product life-cycle.

risk

Combination of the probability of occurrence of harm and severity of the harm.

risk analysis

The estimation of the risk associated with the identified hazards.

risk assessment

A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the evaluation of risk associated with exposure to those hazards.

risk control

The sharing of information about risk and risk management between the decision-maker and other stakeholders.

risk evaluation

The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

risk identification

The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.

risk priority number (RPN)

A numeric assessment of risk assigned to a process, or steps in a process, as part of failure mode effects analysis (FMEA). Each failure mode gets a numeric score that quantifies likelihood of occurrence, likelihood of detection and severity of impact. The product of these three scores is the RPN for that failure mode. $RPN = \text{severity rating} \times \text{occurrence rating} \times \text{detection rating}$.

risk review

Review or monitoring of output or results of the risk management process considering (if appropriate) new knowledge and experience about the risk.

stakeholder

Any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Primary stakeholders are the patient, health-care professional, MRAs and the pharmaceutical industry.

unplanned risk assessment

An assessment that is conducted to assess the impact of a situation that has already occurred, e.g. impact of a deviation from normal ways of working.

validation

The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

verification

The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with the quality risk management activities.

3. Quality risk management process

3.1 Initiating a QRM process

QRM activities should be performed using systematic processes designed to coordinate, facilitate and improve science-based decision-making with respect to risk. The possible steps to be taken in initiating and planning a QRM process might include the following (5):

- define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;
- assemble background information and/or data on the potential hazard, harm or human health impact relevant to the risk assessment;
- identify a leader and the necessary resources;
- specify a timeline, the deliverables, and an appropriate level of decision-making for the risk management process.
- Internal SOPs should define steps, stakeholders, roles and responsibilities (governance and management responsibilities).

3.2 Personnel involved in QRM

The implementing party, i.e. the pharmaceutical manufacturer or regulatory authority, should assure that personnel with appropriate product-specific knowledge and expertise are available to ensure effective planning and completion of QRM activities. This may be best accomplished by assembling a multidisciplinary team according to the guidance provided in section 4.2.

The personnel appointed should be able to:

- conduct a risk analysis;
- identify and analyse potential risks;
- evaluate risks and determine which ones should be controlled and which ones can be accepted;
- recommend and implement adequate risk control measures;
- devise procedures for risk review, monitoring and verification;
- consider the impact of risk findings on related or similar products and/or processes.

QRM activities should be defined and documented.

3.3 Knowledge of the product and process

QRM should be based on knowledge of the product or processes concerned, according to the stage of the product life-cycle.

A flow diagram may be helpful, covering all operations and controls in the process under evaluation. When applying QRM to a given operation, the steps preceding and following that operation should also be considered. A block-type diagram may be sufficiently descriptive. Amendments to the flow diagram may be made where appropriate, and should be documented.

3.4 Risk assessment

When risk assessment is conducted, safety and efficacy need to be considered in addition to the quality concerns.

During the assessment all the risks that may reasonably be expected to occur when conducting the activity under evaluation should be listed. This is usually done when the risk assessment is made for the first time, i.e. initiated, when there is a change or a concern and may also be applied to existing processes. An analysis should be conducted to identify which risks it is essential to eliminate or to reduce to acceptable levels.

A thorough risk assessment is required to ensure effective risk control. Risk assessment should review the materials, operations, equipment, storage, distribution and intended use of the product. Typically a list of the potential risks (biological, chemical and physical) which may be introduced, increased or controlled in each area should be drawn up. In the risk assessment the following basic questions should be addressed:

- What might go wrong?
- What is the nature of possible risks?
- What is the probability of their occurrence and how easy is it to detect them?
- What are the consequences (the severity)?

It should then be decided which of the potential risks should be addressed by the QRM activities and what control measures, if any, should be taken for each risk. If a risk has been identified at a step where control is necessary for safety, and no control measure exists at that step or at any other, the product or process should be modified at that step, or at an earlier or later stage, to include such a control measure. More than one control measure may be required to control a specific risk and more than one risk may be controlled by a specified control measure.

Options for risk assessment methodologies are described in section 5.

Risk assessment can be aided by the use of a decision-tree, which facilitates a logical approach. The way that a decision-tree is used will depend on the operation concerned, e.g. production, packaging, reprocessing, storage or distribution. The best use of QRM tools is discussed further in section 5.

Normally, potential risks in relation to the following should be considered:

- materials and ingredients;
- physical characteristics and composition of the product;
- processing procedures;
- microbial limits, where applicable;
- premises;
- equipment;
- packaging;
- sanitation and hygiene;
- personnel (human error);
- utilities;
- supply chain.

The output of a risk assessment is either a quantitative estimate of risk (numeric probability) or a qualitative description of a range of risk (e.g. high/medium/low) and may be related to a risk matrix (see section 5). The scoring system and trigger points for mitigating action are subjective so the rationale for score categorization should be defined in as much detail as possible. If the score and trigger action are supported by factual evidence it should be more obvious what mitigating action is required – the mitigating action is as important as the score assigned. Professional judgement should be used in interpreting the factual evidence but must be subject to justification.

Records of risk assessments should be maintained.

The expectation of QRM is to assess risks to the product quality and to the patient and then manage these risks so that they are kept at an acceptable level. It is appropriate for companies to assess their control systems so as to implement the appropriate controls to ensure product quality and patient safety. An important principle in QRM is to design risks out of the process or eliminate such risks prospectively, whenever practical and feasible. Risk assessment and mitigation to achieve cost savings, but which could be to the detriment of the well-being of the patient, is an unacceptable practice (9).

3.5 Risk control

Risk control is a decision-making activity designed to reduce and/or accept risks. It usually occurs after risk assessment, and at a fundamental level its purpose is to reduce the risk to an acceptable level.

During risk control activities the following key questions should be asked:

- What can be done to reduce or eliminate risks?
- What is the appropriate balance between benefits, risks and resources?

- Are new risks introduced as a result of the identified risks being controlled?

Risk control can include:

- not proceeding with the risky activity;
- taking the risk;
- removing the risk source;
- changing the likelihood of the risk;
- changing the consequences of the risk;
- sharing the risk with another party (e.g. contractor);
- retaining the risk by informed decision.

Risk control activities usually involve identifying controls and measures which may reduce or control the risk associated with a failure mode or negative event. Risk control activities can serve to determine critical process parameters for certain controls, how they will be monitored, and the level of qualification and validation, if any, which may be required for such controls.

If risk assessments are conducted and risk controls are employed they should be documented. If the risk assessment is conducted for an ongoing activity it should be subject to periodic review and the frequency of review should be appropriate for the nature of the activity.

Based on the criticality or level of risk, specific corrective actions should be developed to prevent recurrence of instances where there have been deviations from established risk control measures, especially for high risks. These actions should ensure that the risk is brought under control as soon as possible in compliance with the established deviation handling procedures.

Specific corrective actions should be developed in advance for each identified risk, including what is to be done when a deviation occurs and who is responsible for implementing the corrective actions. A record should be kept and maintained of the actions taken.

3.6 Risk review

Appropriate systems should be in place to ensure that the output of the QRM process is periodically monitored and reviewed, as appropriate, to assess new information that may impact on the original QRM decision. Examples of such changes include changes to control systems, changes to equipment and processes, changes in suppliers or contractors and organizational restructuring.

Monitoring is the scheduled measurement or observation of a specific risk control measure relative to its acceptance limits. Monitoring should be recorded.

All records and documents associated with risk review should be signed and dated by the person(s) carrying out the review and by a responsible official(s) of the quality unit of the company.

3.7 Verification of QRM process and methodologies

Once in production, the QRM documentation can be integrated into the quality system and used to provide input into the product process.

The established QRM process and methodologies need to be verified. Verification and auditing methods, procedures and tests, including random sampling and analysis, can be used to determine whether the QRM process is working appropriately. The frequency of verification should be sufficient to confirm the proper functioning of the QRM process.

Verification activities include:

- review of the QRM process and its records;
- review of deviations and product dispositions (management control);
- confirmation that identified risks are being kept under control.

Initial verification of the planned QRM activities is necessary to determine whether they are scientifically and technically sound, that all risks have been identified and that, if the QRM activities are properly completed, the risks will be effectively controlled.

Information reviewed to verify the QRM process should include:

- expert advice and scientific studies;
- in-plant observations, measurements and evaluations.

Subsequent verifications should be performed and documented by a QRM team or an independent expert, as needed. For example, verifications may be conducted when there is an unexplained system failure, when a significant change in product, process or packaging occurs or new risks are recognized. Where possible, verification should include actions to confirm the efficacy of all elements of the QRM activities.

In addition, a comprehensive review of the QRM process and specific instances of QRM application by an independent third party may be useful. This would include a technical evaluation of the risk analysis and each element of the QRM process and its application as well as an on-site review of all flow diagrams and appropriate records of the operation of the QRM activity. Such a comprehensive verification is independent of other verification procedures and should be performed to ensure that the QRM process is resulting in the control of the risks. If the results of the comprehensive verification identify deficiencies, the QRM process should be modified as necessary.

Individuals doing verification should have appropriate technical expertise to perform this function.

3.8 Risk communication and documentation

Communication of the QRM process should include key stakeholders. Engaging the key stakeholders in both the data collection process for the risk assessment and the decision-making for risk control will ensure their commitment and support for the QRM. The output of the QRM process and associated risk analysis justifying the approach taken should be documented and endorsed by the organization's quality unit and management. Additionally, this information should be communicated to stakeholders to keep them informed and to ensure their support.

There should be a report for every risk assessment, but the level of effort, formality and documentation necessary will be commensurate with the level of risk (2).

Regarding conclusions of a risk assessment, the mitigation controls should minimize the likelihood of risk to patient safety to an acceptable level of assurance, on the understanding that no risk whatsoever is unlikely in reality. The degree of risk tolerated very much depends on the circumstances, the proximity to the patient and other controls that might follow in response to the process being assessed before the product reaches the patient (2). It is expected that risk mitigation plans will be developed and implemented wherever any risk to patient safety is posed. Companies should take the holistic view and be mindful that critical issues often arise where multiple failures in systems occur together, so mitigation plans should be sufficiently robust to cover this scenario. Inspectors will assess whether risk assessments underrate the likelihood of occurrence and the consequences of overrating detection such that the patient risk is underestimated. The factual evidence behind statements should be robust to challenge by inspectors.

All risk assessments performed by an organization should be documented. The documentation should list and track all key risks as perceived by the organization and summarize how the risks have been mitigated. There should be a clear reference to risk assessments and a list of risk assessments conducted should be maintained. A management process should be in place to review QRM – this may be incorporated into the quality management review process.

4. QRM application for pharmaceuticals

4.1 Training and education

Training of relevant personnel in industry, MRAs and universities in QRM principles and applications is essential for its effective implementation. Industry employees should understand what QRM is, possess the skills necessary to apply it properly, and have access to appropriate resources to enable the effective practice of the QRM principles.

In developing the training programme to support QRM activities, working instructions and procedures should be drawn up which clarify the strategy and define the tasks of all personnel involved in these activities. Specific training should be provided as

required to enhance awareness. Staff with the responsibility for managing and reviewing risks should receive formal training in the relevant procedures.

Cooperation between producers, traders and responsible authorities is vital. Opportunities should be provided for the joint training of industrial staff and MRAs to encourage and maintain a continuous dialogue and create a climate of understanding in the practical application of QRM.

The success of QRM depends on the education and training of management and employees to understand the importance of QRM in producing and supplying safe pharmaceuticals.

4.2 Responsibilities

Successful application of QRM is dependent on a clear understanding of responsibilities by all personnel involved in the QRM activities. It is recommended that a cross-functional matrix of assigned responsibilities and accountabilities is drawn up and shared with all relevant personnel.

The pharmaceutical manufacturer should ensure that appropriate knowledge and expertise are available for the effective planning and completion of QRM activities. QRM activities are usually, but not always, undertaken by a matrix of interdisciplinary teams. When teams are formed they should include experts from the appropriate areas (e.g. quality unit, product development, engineering, regulatory affairs, production operations, statistics, clinical, and others, such as sales, marketing or legal, as applicable), in addition to individuals who are knowledgeable about the QRM process.

In this respect it is acceptable for external consultants to participate in the QRM matrix team where they can provide specific expertise or knowledge. Their role should be justifiable and clearly defined and the resultant accountability must be understood. A technical agreement or other equivalent document with the consultant may be appropriate where a GMP responsibility is assumed.

Similarly, contract staff may become involved in leading or participating in risk assessments, e.g. a contract authorized person. The extent of their involvement and responsibility and accountability must be documented in a technical agreement or other equivalent document between the individual concerned and the pharmaceutical company. Regarding the authorized person it is important that a company's internal procedures are clear on where the responsibility lies for final approval of risk acceptance documents.

Effective matrix team leadership is required to take responsibility for coordinating QRM across various functions and departments of the organization and to ensure that the QRM activities are adequately defined, planned, resourced, deployed and reviewed. The leader and team will need to identify critical resources required to implement the QRM activities, and also specify a timeline, deliverables and appropriate levels of decision-making for the QRM process.

4.3 QRM application during product development

The application of QRM procedures evolves through the various stages in the development of a product.

The first QRM exercise should be performed once the QTPP is defined and preformulation work on the candidate medicine is complete. At this stage of a project there may be significant gaps in knowledge. Therefore, it will be important to apply risk tools that are appropriate for such a situation. These might include:

- cause and effect diagrams (also known as Ishikawa or Fishbone diagrams);
- flowcharts (e.g. input-process-output, IPO);
- decision-trees;
- fault-tree analysis;
- relationship matrices.

As the product progresses to later stage of development, a more detailed analysis of the risks associated with both the active pharmaceutical ingredient (API) and the FPP should be considered. Risks would cover concerns associated with stability, bioavailability and patient safety including any challenges to these areas resulting from the manufacturing process (including, for example, API form conversion under certain conditions of processing).

As product knowledge advances, more detailed QRM exercises can be considered, concentrating on areas considered to present higher priority risk. As the product's critical quality attributes (CQAs) become defined, the potential risks arising from each input material (API, excipients, any device or pack components) and each secondary product unit operation can be investigated.

Eventually, for the developed FPP, the increasingly comprehensive risk assessment will support a thorough understanding of the product and will enable all key variables to be identified, understood and controlled.

4.4 QRM application during validation and qualification

In keeping with the principles of QRM, these guidelines recommend that process validation embraces the product life-cycle concept already mentioned. Accordingly, process validation activities should involve the generation and evaluation of data throughout the process, from development to full-scale production, which will provide a science-based assurance of consistent delivery of quality product in the production operation (9–10).

It is important to emphasize that the building of scientific assurance begins early in development. It is obtained through rational design of experiments and robust evaluation of data during product and process development through to the commercial production phase, by which time the API and FPP CQAs are well understood and controlled. In this scenario, validation or (perhaps more appropriately termed)

conformance batches serve to reinforce the science- or risk-based decisions that have been made as product development has advanced and should demonstrate good control of all critical sources of variability that have been identified. Any unplanned variations within a batch or between batches should be evaluated employing suitable statistical tools, e.g. trend analysis, to check on process control.

A potential advantage of this approach is that there can be flexibility in the number of validation or conformance batches required for regulatory scrutiny prior to approval. The traditional number of batches required for validation has been three but, with QRM embedded in a product's development process, the number of conformance batches needed depends on the depth of knowledge about the process. For very low-volume products, e.g. orphan drugs, this may preclude the need to manufacture multiple batches. It would be beneficial for decisions of this nature regarding conformance batches to have an effective company–MRA dialogue to agree on requirements for a regulatory submission.

When applicable, the principles of QRM should also be applied for qualification activities.

QRM principles can be used to determine the scope of qualification. They can also be used to determine the optimal schedule for maintenance, monitoring, calibration and requalification.

Manufacturers should have sufficient knowledge of the process and product to ensure that by the time the product is commercialized, processes are optimized and risks are minimized.

4.5 QRM application during commercial manufacturing

In general, implementing QRM should not obviate a manufacturer's obligation to comply with regulatory expectations (e.g. regulatory requirements, regulatory filings and inspection commitments). All QRM activities should be structured in a way that allows responsibility for risk assessment and actions at appropriate levels of the hierarchy within the organization. Special focus can be put on the risk assessment and risk control during the life-cycle of a product, and may include:

- product quality risks;
- adverse impact on patient health resulting from product quality defects;
- interruption of product supply to patients;
- GMP and regulatory compliance risks;
- multisite risks;
- multiproduct risks;
- new facility and changes to existing facility, e.g. start-ups, new commercial manufacturing processes, technology transfers and product discontinuation.

After completion of the risk assessment and risk control activities, the outcomes should be summarized and appropriately communicated. The results may be documented in a new or existing report or they may be included as part of another document approved by appropriate decision-makers (e.g. site or functional management, system owner, or quality unit). A risk review is important if new risks or changes to existing risk levels are identified as a result of planned or unplanned events such as routine operation, changes, complaints, product returns, discrepancies or deviations, data monitoring, trends, inspections or audits, or changes in regulatory environment. Risk review may also include evaluation of, for example:

- effectiveness of risk control activities and actions;
- changes in observed risk levels or existing controls.

In principal, areas of focus when implementing QRM in commercial manufacturing include a system focus, a process focus and a product focus.

4.5.1 QRM integration with key quality system elements

Effective QRM can facilitate the decision on “What to do?” and, therefore, support better and more informed decisions. QRM should be integrated into existing quality system elements and related business processes and documented appropriately.

Accordingly, the use of QRM can be beneficial across a broad spectrum of operations, e.g.:

- integrated quality management:
 - documentation
 - training and education
 - quality defects
 - auditing and inspection
 - change management and change control (includes equipment, facilities, utilities, control and IT systems)
 - continual improvement and corrective and preventive actions (CAPA);
- facilities, equipment and utilities:
 - design
 - qualification
 - maintenance and decommissioning of facility or equipment
 - hygiene aspects
 - cleaning of equipment and environmental control

- calibration and preventive maintenance
- computer systems and computer-controlled equipment;
- supplier, materials and contract service management:
 - assessment and evaluation of suppliers and contract manufacturers
 - starting material
 - use of materials
 - storage
 - logistics and distribution conditions;
- technology transfer:
 - from development to manufacturing
 - during commercial manufacturing between sites
 - from commercial manufacturing to product discontinuation.

4.5.2 QRM application in product manufacturing operations

Effective QRM can facilitate the “How to do it?” and, therefore, ensure that the products will meet acceptable standards for safety, quality, and compliance.

Among others, QRM methodology can support the following actions to assess and control quality risks:

- production:
 - manufacturing process risks
 - validation
 - in-process sampling and testing controls
 - production planning
 - deviation and investigation management
 - change management;
- laboratory control and stability studies:
 - out-of-specification results
 - retest period and expiry date
 - method transfers;
- packaging and labelling:
 - design of packages

- selection of container-closure system
- label controls;
- storage, transport and distribution:
 - e.g. cold chain.

5. QRM considerations for medicines regulatory authorities

5.1 Introduction

A key principle of these guidelines is that all MRAs, manufacturing sites in developing countries and API manufacturers should demonstrate, wherever appropriate, application of QRM throughout the product life-cycle for development and manufacturing facilities. Inspectors will review this QRM system as part of the quality systems section of the inspection (along with complaints, recalls, deviations, product quality reviews and others).

Equally, it is recommended that QRM be applied by the MRAs (for examples see (2, 8)) themselves (reviewers and inspectorates) as there are clear benefits of a QRM-based review and inspection plan. For example, inspectors can allocate time and resources commensurate with the perceived significance of risk in any given situation and can be pragmatic regarding the level of scrutiny and degree of formality required.

5.2 QRM application to inspection strategy

5.2.1 Risk management in inspections

The inspection section or unit of an MRA should operate within a written, implemented quality management system (11). SOPs should be followed for activities including (but not limited to) inspection planning, review of corrective and preventive actions after inspections and complaint handling and investigation. Where appropriate, the procedures and activities during inspection should be in line with the principles of QRM.

The unit should have a risk management plan that describes the philosophy, approach, procedures and implementation of risk management. The risk management plan should be reviewed and updated on a continuous basis, or at least annually, and should cover all types of inspections (including GMP, good clinical practices (GCP), good laboratory practices (GLP)) and other activities.

Appropriate risk assessment tools should be used in the process, and the risk assessment for a site to be inspected should be documented on a risk assessment worksheet. Records should be maintained.

A metric system should be used for risk ratings, e.g. on a scale from 1 to 3.

5.2.2 Inspection planning and conduct

The frequency and scope of inspections should be determined based on risk assessment that covers product risk and patient risk.

Risk rating should normally be done only for sites that have been previously inspected. The risk assessment worksheet should be completed after every inspection. Inspection of a site that has not been inspected previously may be waived only in cases where a recognition procedure exists between regulatory inspection units, and where, in addition, appropriate evidence of GXP compliance is available which indicates that there is no risk or an acceptably low risk to products and patients.

Various factors should be considered in the risk assessment exercise, and these factors may be different for the different types of GXP inspections. Risk factors to be considered depend on the type of inspection, and may include:

- outcome of inspection by another regulatory authority;
- outcome of the previous inspection;
- complexity of the site (e.g. buildings, utilities);
- complexity of the product (e.g. sterile, non-sterile);
- type of product (e.g. biological, low-dose);
- complaints and recalls;
- significance of changes (e.g. equipment, key personnel);
- results of product testing;
- risk to the patient;
- complex route of synthesis (API);
- polymorphism (API);
- biopharmaceutical classification of the product;
- innovative or emerging technology.

The number of inspectors and number of days required for the inspection, as well as the scope of the inspection, should be determined based on the risk rating of the site inspection.

Inspection reports should contain findings and observations. Departures from GXP should be classified where appropriate, as “critical”, “major” or “minor”.

The unit should have an SOP that describes the classification process. Classification should be based on risk assessment. The level of risk assigned should be in accordance with the nature of the observation as well as the number of occurrences.

5.2.3 Corrective action and preventive action review, and scheduling of routine inspections

CAPA should be requested from a site, following an inspection. The CAPAs should address the observations included in an inspection report. Based on the outcome of the inspection and the acceptability of the CAPA, the risk rating of the site should be reviewed and recorded.

Inspection frequency should be defined based on the risk rating. For example, the frequency can be defined as every 6, 12, 18 or 24 months. (Note: The maximum time interval should be no more than every 36 months.)

5.2.4 Complaint handling and investigation

Handling and investigation of quality complaints should be done in accordance with a written SOP. The scope and depth of the investigation (including whether a desk review or on-site inspection will be done) should be based on risk assessment.

5.3 Inspection of QRM at a manufacturing site

Note: During inspections, inspectors should assess whether a manufacturer has appropriate skills and scientific knowledge, as well as product and process knowledge, for the QRM procedure being inspected. This is also relevant where a company has made use of contracted parties.

The company's QRM procedure should be appropriately detailed and should be integrated into the company's quality management system. It should cover at least the following areas:

- It should specify the general approach to both planned and unplanned risk assessment, including scope, responsibilities, controls, approvals, management systems, applicability and exclusions.
- Personnel should have appropriate qualifications, experience and training. Their responsibilities with regard to QRM should be clearly defined.
- Senior management should be involved in the identification and implementation of QRM principles within the company.
- The risk management procedure(s) for each area of application should be clearly defined.
- Quality assurance principles should be applied to QRM-related documentation, e.g. review, approval, implementation and archiving.

QRM policies and procedures should be clear and the workflow should be systematic and conducted in a logical order.

- The procedure for risk management should be implemented.

- Manufacturers should identify significant risks and consider all the relevant data from reliable sources.
- The level of effort and resources used in risk assessment should be appropriate to the importance of the identified problem.
- Critical issues should be addressed with appropriate urgency and formality.
- There should be a logical selection of tools for risk assessment.
- Risk acceptance criteria should be appropriate.
- Risk assessments should not underrate the severity, nor overrate detection of occurrences resulting in underestimating patient risk.
- The risk acceptance criteria should be appropriate for the specific situation in question.
- Risk controls should be effective.
- The company should have a review programme to measure the effectiveness of the measures taken.
- Risk-based decision(s) should be science-based and concordant with the predefined acceptance criteria.

All documentation related to the QRM activities should be completed within a reasonable period and should be accessible. Risk assessments performed should be reviewed when appropriate, and additional controls implemented when required.

Personnel should be trained and assessed in the principles of QRM. Where appropriate, a team of members of personnel should participate in the QRM processes.

5.4 QRM applied to dossier review (assessment)

The assessment processes of national medicines regulatory authorities (NMRAs) rely on QRM principles in the management of resources (time and assessors), as well as in the management of product-related risk factors. Efficient management of resources minimizes the risk that limited resources are not used to their best effect, and ultimately ensures that important products are made available in a timely manner. Key factors to be considered include the prioritization of dossiers, the screening process, identification of the specific risk factors inherent to a given dossier or dosage form, and allocation of resources to the various sections of a dossier for a given product. In addition, product-related risk factors must be managed throughout the life-cycle of the product, for example, through effective communication between assessors and inspectors, and by establishing systems for dealing with the products after approval.

The allocation of priority to dossiers should take into account the therapeutic needs of the regional population (e.g. disease occurrence, the need for paediatric formulations, combination products, or experience with innovative or emerging

technology) and the availability of medicines on the market. Prioritization should be a dynamic process to enable it to accommodate emerging issues such as pandemics. Other considerations related to prioritization based on medical need may include fixed-dose combinations versus single-ingredient or co-packaged products, extended release products versus products administered as two or three daily doses, second-line versus first-line products, flexible dosage forms such as dispersible tablets and variable dose products such as oral liquids.

The screening process examines the completeness of a dossier. Screening ensures that only those dossiers that meet minimum standards for completeness can enter into the full assessment process. Insufficient screening processes allow lower quality dossiers to be accepted for review, thus significantly increasing assessment time.

Identification of dossier-related and product-related risk factors allows for the allocation of appropriate resources to specific dossiers. Possible risk factors include: the experience and track record of the manufacturer, narrow therapeutic range products, sterile versus non-sterile APIs and products; API-related considerations such as use of semi-synthetic and fermentation products, complex routes of synthesis, polymorphism, isomerism and potential genotoxic impurities; and product-related considerations such as the use of novel excipients, the complexity of the formulation, single-ingredient versus fixed-dose combinations, and special delivery systems (e.g. modified release, transdermal products, and inhalation products). Once risk factors have been identified, resources should be allocated to minimize risk. For example, assessors with expertise related to the product-related risk identified should be assigned to assess the dossier whenever possible. When resources allow, the assessors may be organized according to specialization, assigning assessors to various product categories (e.g. generic products, sterile products, solid oral dosage forms, or special delivery systems). This can facilitate the development of expertise in key areas and promote consistency of review, as well as ensuring that products requiring specialized knowledge are identified and assessed by those with the appropriate expertise. Where a high level of risk is identified for a dossier, the more experienced assessors need at least to be available on a consultation basis.

The risk level associated with a dossier may change during the course of assessment. For example, rejection of the bioequivalence study will result in additional time required to conduct and assess additional studies and associated additional quality information. In such a scenario the risk relates both to the use of additional resources and to an increased risk that the overall product quality may be poor.

Allocation of resources to various aspects or sections of the dossier is an important QRM consideration, in order to ensure that the resources used are commensurate with the risk level. An understanding of the relative criticality of dossier sections or aspects is necessary for efficient use of resources. All aspects of the dossier are important to achieve overall quality, safety and efficacy; however some areas are inherently more critical from a risk perspective and warrant more attention in the assessment process. Examples include the clinical reviews, bioavailability reviews, API synthesis, specifications and

stability studies, FPP manufacturing details, pharmaceutical development studies including biowaiver justification, process validation, specifications and stability studies. An example applicable to most simple solid oral products is that more time should be allocated to the review of manufacturing steps prior to packaging than to reviewing the packaging process.

During the assessment process there should be a standard procedure for communicating to the inspectors those issues identified which may require consideration during inspection. After approval of a product, QRM principles should be applied to evaluate the impact of proposed variations or changes. Clear guidelines that outline possible post-approval changes and assign an associated risk level are an effective means to achieve this.

6. Risk management tools

A variety of tools can be used for the purposes of QRM, either alone or in combination. It is important to note that no single tool or combination of tools is applicable to every situation in which a QRM procedure is used. Examples of tools are listed in regulatory guidance (6, 8); neither list is exhaustive. The important criterion for acceptability is that the tool or tools are used effectively to support the key attributes of a good risk assessment.

The Product Quality Research Institute (PQRI) Manufacturing Technology Committee (MTC) has produced a summary (9) of common risk management principles and best practices, several working tools to foster consistency in the use of ICH Q9 (5) in day-to-day risk management decision-making, and a series of examples of risk management applications currently in use by major pharmaceutical firms. They have also produced very helpful risk tool training modules for risk ranking and filtering, failure modes effects analysis (FMEA) (12–15), hazard operability analysis (HAZOP) (16) and HACCP (3).

One aspect worth highlighting is the development of a risk matrix to facilitate categorization of risks identified during the risk assessment phase. In order to prioritize a risk, it is essential to agree upon its significance. The risk associated with any situation or event can be represented as the impact of that event multiplied by the probability of its occurrence; in other words: how likely is it to happen? and how severe would it be if it did happen? Impact and probability can each be classified, e.g. into 5 levels (1–5) or with a weighting towards the higher probability and impact ratings (e.g. 1, 3, 5, 7, 10, etc.), so that a grid or matrix can be constructed (Table A3.1).

Table A3.1
An example of a probability versus impact matrix

Probability	Impact				
	Negligible	Marginal	Moderate	Critical	Catastrophic
Almost certain	5	10	15	20	25
Likely	4	8	12	16	20
Possible	3	6	9	12	15
Unlikely	2	4	6	8	10
Rare	1	2	3	4	5

The shading in the table represents an example of how the risk values (sometimes called composite risk indices or risk index values) can be assigned a high, medium or low status. The definition for each status should be predetermined in the QRM process after consideration of the specific consequences for the process undergoing risk assessment. These consequences can be split according to the probability and impact scores, as exemplified in Table A3.2.

Table A3.2
Example of a consequences table for probability and impact

Score	Probability	Example	Score	Impact	Consequence
1	Rare	• Seen every 10–30 years	1	Negligible	<ul style="list-style-type: none"> • No regulatory issue • No effect on and not noticeable by patient
2	Unlikely	• Seen every 5–10 years	2	Marginal	<ul style="list-style-type: none"> • May require MRA notification • Decision to release product not compromised
3	Possible	• Seen every 1–5 years	3	Moderate	<ul style="list-style-type: none"> • MRA inspection may identify a major concern but deficiency quite easily resolved • Limited product recall possible

Table A3.2 continued

Score	Probability	Example	Score	Impact	Consequence
4	Likely	• Seen to occur more than once a year	4	Critical	<ul style="list-style-type: none"> • MRA inspection may conclude serious non-compliance • Likely product recall from one or more markets
5	Almost certain	• Seen several times a year	5	Catastrophic	<ul style="list-style-type: none"> • Enforcement action by MRA such as consent decree, product seizure • Global product recall

MRA, Medicines regulatory authority.

Source: Based on reference 9. This table has been amended, but was originally produced within the context of the Product Quality Research Institute (PQRI), 2107 Wilson Blvd, Suite 700, Arlington, Virginia 22201-3042, USA; web site: <http://www.pqri.org/index.asp>. PQRI has kindly agreed to the use of its material.

This table is a very basic example and would need to be customized for the specific process in question to enable a better and more practical definition of the consequence categories. It should be cautioned that the value of a risk matrix relies very heavily upon input information and should only be used by staff with a good understanding of the embedded judgements and, as such, the resolution of the low, medium or high categorization.

As a summary of the common, well-recognized QRM tool options available for the purposes of these guidelines, Table A3.3 has been based on the one from the Product Quality Research Institute Manufacturing Technology Committee (PQRI-MTC) report (9). The list is not comprehensive but it does include some of the more frequently used approaches.

Table A3.3
Examples of common risk management tools

Risk management tool	Description, attributes	Potential applications
Tools		
Diagram analysis • Flowcharts • Check sheets • Process mapping • Cause/effect diagrams	<ul style="list-style-type: none"> • Simple techniques that are commonly used to gather and organize data, structure risk management processes and facilitate decision-making 	<ul style="list-style-type: none"> • Compilation of observations, trends or other empirical information to support a variety of less complex deviations, complaints, defaults or other circumstances

Table A3.3 continued

Risk management tool	Description, attributes	Potential applications
Tools		
Risk ranking and filtering	<ul style="list-style-type: none"> Method to compare and rank risks Typically involves evaluation of multiple diverse quantitative and qualitative factors for each risk, and weighting factors and risk score 	<ul style="list-style-type: none"> Prioritizing operating areas or sites for audit or assessment Useful for situations when the risks and underlying consequences are diverse and difficult to compare using a single tool
Fault-tree analysis	<ul style="list-style-type: none"> Method used to identify all root causes of an assumed failure or problem Used to evaluate system or subsystem failures one at a time, but can combine multiple causes of failure by identifying causal chains Relies heavily on full process understanding to identify causal factors 	<ul style="list-style-type: none"> Investigate product complaints Evaluate deviations
Hazard operability analysis (HAZOP)	<ul style="list-style-type: none"> Tool assumes that risk events are caused by deviations from the design and operating intentions Uses a systematic technique to help identify potential deviations from normal use or design intentions 	<ul style="list-style-type: none"> Access manufacturing processes, suppliers, facilities and equipment Commonly used to evaluate process safety hazards
Hazard analysis and critical control point (HACCP)	<ul style="list-style-type: none"> Identify and implement process controls that consistently and effectively prevent hazard conditions from occurring Bottom-up approach that considers how to prevent hazards from occurring and/or propagating Emphasizes strength of preventive controls rather than ability to detect 	<ul style="list-style-type: none"> Better for preventive applications than reactive Valuable precursor or complement to process validation Assessment of the efficacy of critical control points and the ability to consistently execute them for any process

Table A3.3 *continued*

Risk management tool	Description, attributes	Potential applications
Tools		
Failure modes effects analysis (FMEA)	<ul style="list-style-type: none"> Assumes comprehensive understanding of the process and that CPPs have been defined prior to initiating the assessment. Tool ensures that CPPs will be met. Assesses potential failure modes for processes, and the probable effect on outcomes and/or product performance Once failure modes are known, risk reduction actions can be applied to eliminate, reduce or control potential failures 	<ul style="list-style-type: none"> Evaluate equipment and facilities; analyse a manufacturing process to identify high risk steps and/or critical parameters
Failure modes effects analysis (FMEA)	<ul style="list-style-type: none"> Highly dependent upon strong understanding of product, process and/or facility under evaluation Output is a relative "risk score" for each failure mode 	

Source: Based on reference 9. This table has been amended, but was originally produced within the context of the Product Quality Research Institute (PQRI), 2107 Wilson Blvd, Suite 700, Arlington, Virginia 22201-3042, USA; web site: <http://www.pqri.org/index.asp>. PQRI has kindly agreed to the use of its material.

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Further reading

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4.6 Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance

Annex 6, WHO Technical Report Series, 1025, 2020 (new)

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1. Introduction and scope

1.1 Background

According to research by UN Environment (1), growing antimicrobial resistance (AMR) linked to the discharge of drugs and particular chemicals into the environment is one of the most worrying health threats of today. AMR accounts for an estimated 700 000 deaths per year worldwide and, by 2030, will represent up to US\$ 3.4 trillion in gross domestic product (GDP) loss (2). AMR has been identified as a priority at the World Health Assembly since 1998 (3), with rising momentum throughout the years. Since 1998, there have been a series of World Health Assembly resolutions on AMR. These paved the way to the Sixty-eighth World Health Assembly in May 2015, where the World Health Assembly endorsed a global action plan to tackle AMR, including antibiotic resistance, the most urgent drug resistance trend (4). More recently, the *Thirteenth General Programme of Work (2019–2023)* highlighted the need to address this emerging threat, under the section for “Tackling antimicrobial resistance” (2). It is only recently that the need to address waste and wastewater management from pharmaceutical production has been explicitly addressed. Namely, on 30 November 2018, the World Health Organization’s (WHO’s) Executive Board meeting decided that technical input will be provided to good manufacturing practices (GMP) guidance on waste and wastewater management from the production of critically important antimicrobials (5, 6). The present *Points to consider* document was written further to this recent decision.

We are entering a post-antibiotic era, where simple and previously treatable bacterial infections can kill and where routine medical procedures that rely on antibiotic preventative treatment, such as joint replacements and chemotherapy, will not be possible. The 2014 O’Neill report commissioned by the Government of the United Kingdom of Great Britain and Northern Ireland estimated that antimicrobial-resistant infections may become the leading cause of death globally by 2050 (7).

The environment plays an important role in antimicrobial resistance. Microorganisms in soil, rivers and seawater can develop resistance through contact with resistant microbes (transfer of resistance genes), antibiotics and disinfectant agents released by human activity (1), as well as heavy metals (8, 9) that may propagate AMR in the environment. People and livestock could then be exposed to more resistant bacteria through food, water and air (1).

Pharmaceuticals entering the environment from industrial manufacturing activities are not the major source of antimicrobial resistance, but in countries that contribute the most to the production of antimicrobials, this issue can be significant. The levels of pollution with antimicrobials have been measured in waters in the proximity of pharmaceutical production facilities. Antimicrobial concentrations in some effluents are too low to be lethal to exposed bacteria but may still be sufficient to induce antimicrobial resistance (1, 10), but high concentrations have been found downstream

of antimicrobial manufacturing sites in several countries. Scientific literature reports a correlation between the type and number of highly resistant bacteria and the level of antimicrobial pollution (10). This led to manufacturing sites being identified as one of the hot spots for development of AMR, but this knowledge dates from only a few years ago (11).

Poor control of waste (solid¹ or liquid) and wastewater, such as that encountered in some of the countries that are major global producers of pharmaceuticals, can often lead to the entry of antimicrobials into waters that are contaminated with pathogenic bacteria from untreated sewage. This increases the risk of development of AMR. Furthermore, a vast array of contaminants in municipal and industrial wastewater increases pressure on bacteria to become resistant (1, 11). Eventually, from the passage of the production cycle to the effluent pipe, antimicrobial molecules (precursors and by-products) turn from valuable medicine to hazardous waste that has an impact on the efficacy of the product as well as human health and the environment.

Concentrations in river water depend on wastewater treatment facilities, as well as antimicrobial use in the populations they serve. Treatment plants are generally designed to remove conventional pollutants such as nutrients, organic matter, suspended solids and pathogens, but not pharmaceuticals such as antimicrobial agents (1). The level of treatment of manufacturing effluents or pharmaceutical waste (solid or liquid) can vary significantly, resulting in the necessity for municipal wastewater treatment plants to handle the waste. However, the activated waste may up-concentrate some antimicrobial agents, as well as antimicrobial-resistant bacteria, increasing the risk for AMR in environments where the sludge is applied. Recent evidence indicates the presence of a selection pressure for AMR within environments receiving wastewater from antimicrobial manufacturing, as opposed to environments receiving wastewater from municipal sewage treatment plants (12) that do not receive waste from antimicrobial manufacturing.

It is therefore important to significantly reduce the concentration of antimicrobials prior to disposal into the environment. However, the recommended approach in the absence of established standards would be to apply the precautionary principle, i.e. to not emit any waste until there is proof that the discharge does not have an adverse effect on human health or the environment.

Several initiatives have already been put in place by the United Nations (13, 14), WHO (4), nongovernmental institutions (15–17), governments (18–24) and the industry itself (25–29). Industry should be committed to caring for the environment, and responsible manufacturing is encouraged by taking steps to minimize the environmental impact of operations and products, while also balancing the need to produce high-quality, life-saving medication.

¹ Solid waste is also considered in this document because, if not properly disposed of, different types of solid waste may leach into the surrounding environment and contaminate effluents.

This document is to be considered as a time-limited document that addresses the current needs for guidance on how GMP should be implemented to waste and wastewater management for production of antimicrobials. It leverages on the existing GMP and makes reference to relevant literature rather than containing detailed instructions. This document may be updated in the future, as the knowledge about suitable technologies on how to remove antimicrobial residues is expected to increase within the next few years and the requirements may be modified/adapted in consequence.

1.2 Purpose

The purpose of this document is to:

- provide recommendations and expectations for manufacturing facilities for medicines regarding waste management, to mitigate/prevent potential antimicrobial resistance;
- raise awareness of medicines' manufacturers, national regulatory authorities (NRAs) and especially GMP inspectorates and inspectors in all Member States, on sections of relevant GMP guidance that are applicable to the management of waste/wastewater from the production of antimicrobials, while emphasizing the importance of all aspects of GMP implementation and considering the parts of GMP that may not have a direct impact on product quality; and
- provide clarification on the interpretation of those clauses and specific measures that should be taken to be considered compliant with the relevant sections of GMP guidance, without changing the scope of GMP.

This document is not intended to cover AMR issues that are related to the human or veterinary use of antimicrobials or to other types of environmental contamination (1), such as the excretion of antimicrobials during their use. It should not be considered to provide exhaustive information on methods that can be used to control and reduce contamination of the environment with antimicrobials and related chemicals, such as active precursors or by-products coming from pharmaceutical production processes. It should also not be considered to provide information on the levels of antimicrobial residues that are considered acceptable.

1.3 Target audience

This document is targeted to:

- all pharmaceutical manufacturers engaging in synthesis and/or production of antimicrobials (primarily manufacturing sites for active pharmaceutical ingredients [APIs] and, secondly, manufacturing sites for finished pharmaceutical products [FPPs]);

- GMP inspectors and inspectorates from national medicines regulatory authorities;
- regulatory bodies that are responsible for enforcing environmental protection standards and waste/wastewater management in all Member States – consistent with a multidisciplinary approach, including but not limited to ministries of health, ministries of environment or pollution control boards, and ministries of agriculture, as appropriate; and
- waste and wastewater management services that handle antimicrobial waste and/or process effluents from the pharmaceutical industry.

2. Glossary

The definitions given below apply to the terms as used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts.

active pharmaceutical ingredient (API). Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

antimicrobial resistance (AMR). Antibiotic resistance develops when bacteria adapt and grow in the presence of antibiotics. The development of resistance is linked to how often antibiotics are used. Because many antibiotics belong to the same class of medicines, resistance to one specific antibiotic agent can lead to resistance to a whole related class. Resistance that develops in one organism or location can also spread rapidly and unpredictably through, for instance, the exchange of genetic material between different bacteria, and can affect antibiotic treatment of a wide range of infections and diseases. Drug-resistant bacteria can circulate in populations of human beings and animals, through food, water and the environment, and transmission is influenced by trade, travel and both human and animal migration. Resistant bacteria can be found in food, animals and food products destined for consumption by humans. Some of these features also apply to medicines that are used to treat viral, parasitic and fungal diseases, hence the broader term antimicrobial resistance.

finished pharmaceutical product (FPP). A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

3. Review of the environmental aspects of good manufacturing practices

GMP are, a priori, intended to control the manufacture of medicines, and in principle do not focus on the environmental aspects of these. However, GMP include many aspects related to the protection of the environment and workers. If fully implemented, GMP should therefore prevent many different types of waste from contaminating the environment.

Given that the lack of control in the downstream processes of manufacturing medicines will ultimately lead to their loss in efficacy, we may no longer focus only on the aspects of GMP that are directly linked to the quality of medicines. Medicines that are no longer effective lose their value and it is therefore crucial for manufacturers and all stakeholders to take action in order to protect the efficacy of those medicines. Only one major class of antibiotics has been discovered since 1987 (30) and too few antibacterial agents are in development to meet the challenge of multidrug resistance (4).

The *WHO good manufacturing practices for pharmaceutical products: main principles* (31) and *WHO good manufacturing principles for active pharmaceutical ingredients* (32) contain a limited set of clauses related to environmental issues. Waste and wastewater management are addressed only briefly. The following clauses are the only ones considered to be of relevance:

WHO good manufacturing practices for pharmaceutical products: main principles. Annex 2, WHO Technical Report Series, No. 986, 2014 (31)

Waste materials

- 14.44 *Provisions should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.*
- 14.45 *Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.*

WHO good manufacturing practices for active pharmaceutical ingredients. Annex 2, WHO Technical Report Series, No. 957, 2010 (32)

4.6 Sewage and refuse

- 4.60 *Sewage, refuse and other waste (e.g. solids, liquids or gaseous by-products from manufacturing) in and from buildings and the immediate*

surrounding area should be disposed of in a safe, timely and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

On the other hand, the *WHO good manufacturing practices for pharmaceutical products containing hazardous substances* (33) contains more detailed requirements regarding waste and wastewater management, which can be applied to the production of antimicrobials. These guidelines cover those hazardous substances traditionally belonging to reproductive health hormones and highly potent materials such as steroids or sensitizing medicines such as beta-lactam antibiotics. According to these guidelines, a hazardous substance or product is a “product or substance that may present a substantial risk of injury, to health or to the environment”. As antimicrobials are deemed to present a substantial risk of injury to both health and the environment, when released into the environment through their action on microorganisms, they should be considered for inclusion in the scope of this guidance.

The following clause is considered to be of general relevance to the protection of the operators, the environment and the public:

WHO good manufacturing practices for pharmaceutical products containing hazardous substances. Annex 3, WHO Technical Report Series, No. 957, 2010 (33)

General

2.1 *Facilities should be designed and operated in accordance with the main GMP principles, as follows:*

- to ensure quality of product;*
- to protect the operators from possible harmful effects of products containing hazardous substances; and*
- to protect the environment from contamination and thereby protect the public from possible harmful effects of products containing hazardous substances.*

The guidelines require risk assessments to determine the potential hazards to the operators and to the environment of hazardous substances contained in all types of waste, as per the following clauses:

Risk assessment

4.1 *Not all products containing hazardous substances are equally potent and risk assessments should be carried out to determine the potential hazards to operators and to the environment. The risk assessment should also*

determine which phases of the product production and control cycles, from manufacture of the API to distribution of the finished product, would fall under the requirements of these guidelines. Risk assessments applicable to the environment should include airborne contamination as well as liquid effluent contamination.

- 4.2 *Assuming that the risk assessment determines that the products or materials being handled pose a risk to the operators and/or the public and/or the environment, the guidelines to be followed for the design and operation of the facility should be as detailed in this document.*

Such risk assessments should therefore be performed by manufacturers as required, in principle, for any substance deemed to be hazardous.

The guidance already has a requirement prohibiting discharge of hazardous substances into normal drainage systems:

Environmental protection

- 7.1 *Due to the hazardous nature of the products being handled in the facility, neither the product nor its residues should be allowed to escape into the atmosphere or to be discharged directly to normal drainage systems.*

It also has a requirement for protection of the atmosphere and the public in the local vicinity:

- 7.2 *The external atmosphere and the public in the vicinity of the facility should be protected from possible harm from hazardous substances.*

The above clause may be considered to apply to effluents and water streams near facilities, as their contamination with antimicrobials can have a public health impact. The literature contains several reports of effluents and water streams contaminated with potentially dangerous levels of antimicrobials (8, 10, 12).

The guidance also has a requirement for treatment of hazardous effluent before it is discharged:

- 7.3 *If liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain.*

However, it should be noted that the municipal drain may not be suitable to handle the large quantities of hazardous effluents such as those that are released by large pharmaceutical companies, and therefore manufacturers are requested to carefully consider this in their approach.

The guidance also contains a general statement about handling of liquid and solid waste effluent and another about safe disposal:

13. Effluent treatment

- 13.1 *Liquid and solid waste effluent should be handled in such a manner as not to present a risk of contamination to the product, personnel or to the environment.*
- 13.2 *All effluent should be disposed of in a safe manner, and the means of disposal should be documented. Where external contractors are used for effluent disposal they should have certification authorizing them to handle and treat hazardous products.*

As per the above clause, where external contractors are used for effluent disposal, they should have certification authorizing them to handle and treat hazardous products.

The management of waste that is obtained from quality control testing in a laboratory setting at a manufacturer's site or contract laboratory is covered by the following clause:

Guidance on good practices for pharmaceutical quality control laboratories. Annex 1, WHO Technical Report Series, No. 957, 2010 (34)

7. Premises

- 7.6 *Procedures should be in place for the safe removal of types of waste including toxic waste (chemical and biological), reagents, samples, solvents and air filters.*

The amount of antimicrobial waste being generated by laboratory testing activities is generally considered to be negligible compared to the amounts that are being generated by manufacturing activities but should still be considered in exceptional cases, e.g. if very large amounts of sample are being tested by a quality control laboratory.

4. Expectations for manufacturers of antimicrobials

Application of the requirements outlined in the above-mentioned GMP clauses shall be verified during onsite inspections. In addition, manufacturers of APIs and FPPs should consider retaining documentation on the following:

- a risk assessment for all contaminants related to antimicrobial manufacturing, in the event that they are released into the environment, and the associated risk of development of resistant microorganisms;
- based on the above risk assessment, waste-stream analysis for each antimicrobial agent produced (at API sites and FPP sites). This analysis should be repeated whenever there is a change in production affecting waste streams;

- the quantity and nature of the waste generated, including the analytical data and documentation of analyses performed and their findings on the levels of antimicrobial agents or their precursors;
- regular reports on the collection, treatment and disposal of waste and wastewater; the frequency should be risk-based and in line with local, regional or international regulatory requirements, as applicable;
- information on the methods used to treat the waste should be documented to be effective for each specific antimicrobial or antimicrobial precursor. Analytical data demonstrating the conversion of these substances and their residues to non-hazardous waste materials should be available at the facility and kept up to date;
- if effective waste treatment is not yet implemented for all waste streams resulting from the manufacture of each API or FPP, documentation on a time-limited strategy should be in place, with specified milestones for that implementation, specifying actions towards achieving treatment that significantly reduces the concentration of the antimicrobial substance or its precursor (and its microbial source, when relevant); and
- a rationale and risk assessment as to why the manufacturer selected specific methods of decontamination of manufacturing waste containing antimicrobials and/or their mitigation strategy. Many decontamination methods already exist that reduce or remove antimicrobials (and microbes that have produced fermentative antimicrobials) from waste streams entering the environment from antimicrobial manufacturing: secondary and tertiary wastewater treatment; membrane filtration and ozonation; and ultraviolet disinfection and heat treatment, which are even more effective at removing viable bacteria (1, 11). Incineration may also be considered for solid or semi-liquid waste. The zero-liquid effluent approach or zero-discharge policy is encouraged, especially when the risk is assessed to be high or unclear, as it prevents any contamination of the environment. The level of effectiveness and by-products should be considered when adopting a particular approach.

It is recommended that this documentation be maintained at the manufacturing facility regardless of whether or not an external contractor has been used. These points to consider should be used by manufacturers as part of their self-audits, in order to verify their continued level of GMP compliance. Although the aim is not to reduce verification of the quality of products, the waste management practices and related documentation listed in this *Points to consider* document could be reviewed and scrutinized during regulatory inspections.

It should be noted that the above requirements will not be used to draw a conclusion on the level of GMP compliance of a manufacturing site. Their purpose is to

guide/encourage manufacturers to apply all of the GMP principles. The application of these principles will help to tackle the emergence of AMR, by raising awareness of the preventative measures that manufacturers should take to adequately manage the waste and wastewaters that are generated while manufacturing antimicrobials.

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4.7 Guideline on data integrity

Annex 4, WHO Technical Report Series, 1033, 2021 (revised)

This document replaces the WHO *Guidance on good data and record management practices* (Annex 5, WHO Technical Report Series, No. 996, 2016) (1).

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1. Introduction and background

- 1.1 In recent years, the number of observations made regarding the integrity of data, documentation and record management practices during inspections of good manufacturing practice (GMP) (2), good clinical practice (GCP), good laboratory practice (GLP) and Good Trade and Distribution Practices (GTDP) have been increasing. The possible causes for this may include (i) reliance on inadequate human practices; (ii) poorly defined procedures; (iii) resource constraints; (iv) the use of computerized systems that are not capable of meeting regulatory requirements or are inappropriately managed and validated (3, 4); (v) inappropriate and inadequate control of data flow; and (vi) failure to adequately review and manage original data and records.
- 1.2 Data governance and related measures should be part of a quality system, and are important to ensure the reliability of data and records in good practice (GxP) activities and regulatory submissions. The data and records should be ‘attributable, legible, contemporaneous, original’ and accurate, complete, consistent, enduring, and available; commonly referred to as “ALCOA+”.
- 1.3 This document replaces the WHO *Guidance on good data and record management practices* (Annex 5, WHO Technical Report Series, No. 996, 2016) (1).

2. Scope

- 2.1 This document provides information, guidance and recommendations to strengthen data integrity in support of product quality, safety and efficacy. The aim is to ensure compliance with regulatory requirements in, for example clinical research, production and quality control, which ultimately contributes to patient safety. It covers electronic, paper and hybrid systems.
- 2.2 The guideline covers "GxP" for medical products. The principles could also be applied to other products such as vector control products.
- 2.3 The principles of this guideline also apply to contract givers and contract acceptors. Contract givers are ultimately responsible for the integrity of data provided to them by contract acceptors. Contract givers should therefore ensure that contract acceptors have the appropriate capabilities and comply with the principles contained in this guideline and documented in quality agreements.
- 2.4 Where possible, this guideline has been harmonised with other published documents on data integrity. This guideline should also be read with other WHO good practices guidelines and publications including, but not limited to, those listed in the references section of this document.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

ALCOA+. A commonly used acronym for “attributable, legible, contemporaneous, original and accurate” which puts additional emphasis on the attributes of being complete, consistent, enduring and available throughout the data life cycle for the defined retention period.

Archiving. Archiving is the process of long-term storage and protection of records from the possibility of deterioration, and being altered or deleted, throughout the required retention period. Archived records should include the complete data, for example, paper records, electronic records including associated metadata such as audit trails and electronic signatures. Within a GLP context, the archived records should be under the control of independent data management personnel throughout the required retention period.

Audit trail. The audit trail is a form of metadata containing information associated with actions that relate to the creation, modification or deletion of GxP records. An audit trail provides for a secure recording of life cycle details such as creation, additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or overwriting the original record. An audit trail facilitates the reconstruction of the history of such events relating to the record regardless of its medium, including the “who, what, when and why” of the action.

Backup. The copying of live electronic data, at defined intervals, in a secure manner to ensure that the data are available for restoration.

Certified true copy or true copy. A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Data. All original records and true copies of original records, including source data and metadata, and all subsequent transformations and reports of these data which are generated or recorded at the time of the GMP activity and which allow full and complete reconstruction and evaluation of the GMP activity. Data should be accurately recorded by permanent means at the time of the activity. Data may be contained in paper records (such as worksheets and logbooks), electronic records and audit trails, photographs, microfilm or microfiche, audio or video files or any other media whereby information related to GMP activities is recorded.

Data criticality. This is defined by the importance of the data for the quality and safety of the product and how important data are for a quality decision within production or quality control.

Data governance. The sum total of arrangements which provide assurance of data quality. These arrangements ensure that data, irrespective of the process, format or technology in which it is generated, recorded, processed, retained, retrieved and used will ensure an attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available record throughout the data life cycle.

Data integrity risk assessment (DIRA). The process to map out procedures, systems and other components that generate or obtain data; to identify and assess risks and implement appropriate controls to prevent or minimize lapses in the integrity of the data.

Data life cycle. All phases of the process by which data are created, recorded, processed, reviewed, analysed and reported, transferred, stored and retrieved and monitored, until retirement and disposal. There should be a planned approach to assessing, monitoring and managing the data and the risks to those data, in a manner commensurate with the potential impact on patient safety, product quality and/or the reliability of the decisions made throughout all phases of the data life cycle.

Dynamic data. Dynamic formats, such as electronic records, allow an interactive relationship between the user and the record content. For example, electronic records in database formats allow the user to track, trend and query data; chromatography records maintained as electronic records allow the user or reviewer (with appropriate access permissions) to reprocess the data and expand the baseline to view the integration more clearly.

Electronic signatures. A signature in digital form (bio-metric or non-biometric) that represents the signatory. In legal terms, it is the equivalent of the handwritten signature of the signatory.

Good practices (GxP). An acronym for the group of good practice guides governing the preclinical, clinical, manufacturing, testing, storage, distribution and post-market activities for regulated pharmaceuticals, biologicals and medical devices, such as GLP, GCP, GMP, good pharmacovigilance practices (GVP) and good distribution practices (GDP).

Hybrid system. The use of a combination of electronic systems and paper systems.

Medical product. A term that includes medicines, vaccines, diagnostics and medical devices.

Metadata. Metadata are data that provide the contextual information required to understand other data. These include structural and descriptive metadata, which describe

the structure, data elements, interrelationships and other characteristics of data. They also permit data to be attributable to an individual. Metadata that are necessary to evaluate the meaning of data should be securely linked to the data and subject to adequate review. For example, in the measurement of weight, the number 8 is meaningless without metadata, such as, the unit, milligram, gram, kilogram, and so on. Other examples of metadata include the time or date stamp of an activity, the operator identification (ID) of the person who performed an activity, the instrument ID used, processing parameters, sequence files, audit trails and other data required to understand data and reconstruct activities.

Raw data. The original record (data) which can be described as the first-capture of information, whether recorded on paper or electronically. Raw data is synonymous with source data.

Static data. A static record format, such as a paper or electronic record, that is fixed and allows little or no interaction between the user and the record content. For example, once printed or converted to static electronic format chromatography records lose the capability of being reprocessed or enabling more detailed viewing of baseline.

4. Data governance

- 4.1 There should be a written policy on data integrity.
- 4.2 Senior management should be accountable for the implementation of systems and procedures in order to minimise the potential risk to data integrity, and to identify the residual risk using risk management techniques such as the principles of the guidance on quality risk management from WHO (5) and The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (6).
- 4.3 Senior management is responsible for the establishment, implementation and control of an effective data governance system. Data governance should be embedded in the quality system. The necessary policies, procedures, training, monitoring and other systems should be implemented.
- 4.4 Data governance should ensure the application of ALCOA+ principles.
- 4.5 Senior management is responsible for providing the environment to establish, maintain and continually improve the quality culture, supporting the transparent and open reporting of deviations, errors or omissions and data integrity lapses at all levels of the organization. Appropriate, immediate action should be taken when falsification of data is identified. Significant lapses in data integrity that may impact patient safety, product quality or efficacy should be reported to the relevant medicine regulatory authorities.

- 4.6 The quality system, including documentation such as procedures and formats for recording and reviewing of data, should be appropriately designed and implemented in order to provide assurance that records and data meet the principles contained in this guideline.
- 4.7 Data governance should address the roles, responsibilities, accountability and define the segregation of duties throughout the life cycle and consider the design, operation and monitoring of processes/systems to comply with the principles of data integrity, including control over authorized and unauthorized changes to data.
- 4.8 Data governance control strategies using quality risk management (QRM) principles (5) are required to prevent or mitigate risks. The control strategy should aim to implement appropriate technical, organizational and procedural controls. Examples of controls may include, but are not limited to:
 - the establishment and implementation of procedures that will facilitate compliance with data integrity requirements and expectations;
 - the adoption of a quality culture within the company that encourages personnel to be transparent about failures, which includes a reporting mechanism inclusive of investigation and follow-up processes;
 - the implementation of appropriate controls to eliminate or reduce risks to an acceptable level throughout the life cycle of the data;
 - ensuring sufficient time and resources are available to implement and complete a data integrity programme; to monitor compliance with data integrity policies, procedures and processes through e.g. audits and self-inspections; and to facilitate continuous improvement of both;
 - the assignment of qualified and trained personnel and provision of regular training for personnel in, for example, GxP, and the principles of data integrity in computerized systems and manual/paper based systems;
 - the implementation and validation of computerized systems appropriate for their intended use, including all relevant data integrity requirements in order to ensure that the computerized system has the necessary controls to protect the electronic data (3); and
 - the definition and management of the appropriate roles and responsibilities for contract givers and contract acceptors, entered into quality agreements and contracts including a focus on data integrity requirements.
- 4.9 Data governance systems should include, for example:
 - the creation of an appropriate working environment;

- active support of continual improvement in particular based on collecting feedback; and
 - review of results, including the reporting of errors, unauthorized changes, omissions and undesirable results.
- 4.10 The data governance programme should include policies and procedures addressing data management. These should at least where applicable, include:
- management oversight and commitment;
 - the application of QRM;
 - compliance with data protection legislation and best practices;
 - qualification and validation policies and procedures;
 - change, incident and deviation management;
 - data classification, confidentiality and privacy;
 - security, cybersecurity, access and configuration control;
 - database build, data collection, data review, blinded data, randomization;
 - the tracking, trending, reporting of data integrity anomalies, and lapses or failures for further action;
 - the prevention of commercial, political, financial and other organizational pressures;
 - adequate resources and systems;
 - workload and facilities to facilitate the right environment that supports DI and effective controls;
 - monitoring;
 - record-keeping;
 - training; and
 - awareness of the importance of data integrity, product quality and patient safety.
- 4.11 There should be a system for the regular review of data for consistency with ALCOA+ principles. This includes paper records and electronic records in day-to-day work, system and facility audits and self-inspections.
- 4.12 The effort and resources applied to assure the integrity of the data should be commensurate with the risk and impact of a data integrity failure.
- 4.13 Where weaknesses in data integrity are identified, the appropriate corrective and preventive actions (CAPA) should be implemented across all relevant activities and systems and not in isolation.

4.14 Changing from paper-based systems to automated or computerised systems (or vice-versa) will not in itself remove the need for appropriate data integrity controls.

4.15 Records (paper and electronic) should be kept in a manner that ensures compliance with the principles of this guideline. These include but are not limited to:

- ensuring time accuracy of the system generating the record, accurately configuring and verifying time zone and time synchronisation, and restricting the ability to change dates, time zones and times for recording events;
- using controlled documents and forms for recording GxP data;
- defining access and privilege rights to GxP automated and computerized systems, ensuring segregation of duties;
- ensuring audit trail activation for all interactions and restricting the ability to enable or disable audit trails (Note: ‘back-end’ changes and ‘hard’ changes, such as hard deletes, should not be allowed). Where audit trials can be disabled then this action should also appear in the audit trail;
- having automated data capture systems and printers connected to equipment and instruments in production (such as Supervisory Control and Data Acquisition (SCADA), Human Machine Interface (HMI) and Programme Logic Control (PLCs) systems), in , quality control, and in clinical research (such as Clinical Data Management (CDM) systems), where possible;
- designing processes in a way to avoid the unnecessary transcription of data or unnecessary conversion from paper to electronic and vice versa; and
- ensuring the proximity of an official GxP time source to site of GxP activity and record creation.

4.16 Systems, procedures and methodology used to record and store data should be periodically reviewed for effectiveness. These should be updated throughout the data life cycle, as necessary, where new technology becomes available. New technology implementation must be evaluated before implementation to verify the impact on data integrity.

5. Quality risk management

Note: documentation of data flows and data process maps are recommended to facilitate the assessment, mitigation and control of data integrity risks across the actual and intended data process(es).

- 5.1 Data Integrity Risk Assessment (DIRA) should be carried out in order to identify and assess areas of risk. This should cover systems and processes that produce data or, where data are obtained and inherent risks. The DIRAs should be risk-based, cover the life cycle of data and consider data criticality. Data criticality may be determined by considering how the data is used to influence the decisions made. The DIRAs should be documented and reviewed, as required, to ensure that it remains current.
- 5.2 The risk assessments should evaluate, for example, the relevant GxP computerised systems, supporting personnel, training, quality systems and outsourced activities.
- 5.3 DI risks should be assessed and mitigated. Controls and residual risks should be communicated. Risk review should be done throughout the document and data life cycle at a frequency based on the risk level, as determined by the risk assessment process.
- 5.4 Where the risk assessment has highlighted areas for remedial action, the prioritisation of actions (including the acceptance of an appropriate level of residual risk) and the prioritisation of controls should be documented and communicated. Where long-term remedial actions are identified, risk-reducing short-term measures should be implemented in order to provide acceptable data governance in the interim.
- 5.5 Controls identified may include organizational, procedural and technical controls such as procedures, processes, equipment, instruments and other systems in order to both prevent and detect situations that may impact on data integrity. Examples include the appropriate content and design of procedures, formats for recording, access control, the use of computerized systems and other means.
- 5.6 Efficient risk-based controls should be identified and implemented to address risks impacting data integrity. Risks include, for example, the deletion of, changes to and exclusion of data or results from data sets without written justification, authorisation where appropriate, and detection. The effectiveness of the controls should be verified (see Appendix 1 for examples).

6. Management review

- 6.1 Management should ensure that systems (such as computerized systems and paper systems) are meeting regulatory requirements in order to support data integrity compliance.
- 6.2 The acquisition of non-compliant computerized systems and software should be avoided. Where existing systems do not meet current requirements, appropriate controls should be identified and implemented based on risk assessment.

6.3 The effectiveness of the controls implemented should be evaluated through, for example:

- the tracking and trending of data;
- a review of data, metadata and audit trails (e.g. in warehouse and material management, production, quality control, case report forms and data processing); and
- routine audits and/or self-inspections, including data integrity and computerized systems.

7. Outsourcing

- 7.1 The selection of a contract acceptor should be done in accordance with an authorized procedure. The outsourcing of activities, ownership of data, and responsibilities of each party (contract giver and contract accepter) should be clearly described in written agreements. Specific attention should be given to ensuring compliance with data integrity requirements. Provisions should be made for responsibilities relating to data when an agreement expires.
- 7.2 Compliance with the principles and responsibilities should be verified during periodic site audits. This should include the review of procedures and data (including raw data and metadata, paper records, electronic data, audit trails and other related data) held by the relevant contract accepter identified in risk assessment.
- 7.3 Where data and document retention are contracted to a third party, particular attention should be given to security, transfer, storage, access and restoration of data held under that agreement, as well as controls to ensure the integrity of data over their life cycle. This includes static data and dynamic data. Mechanisms, procedures and tools should be identified to ensure data integrity and data confidentiality, for example, version control, access control, and encryption.
- 7.4 GxP activities, including outsourcing of data management, should not be subcontracted to a third party without the prior approval of the contract giver. This should be stated in the contractual agreements.
- 7.5 All contracted parties should be aware of the requirements relating to data governance, data integrity and data management.

8. Training

- 8.1 All personnel who interact with GxP data and who perform GxP activities should be trained in relevant data integrity principles and abide by organization policies

and procedures. This should include understanding the potential consequences in cases of non-compliance.

- 8.2 Personnel should be trained in good documentation practices and measures to prevent and detect data integrity issues.
- 8.3 Specific training should be given in cases where computerized systems are used in the generation, processing, interpretation and reporting of data and where risk assessment has shown that this is required to relevant personnel. Such training should include validation of computerized systems and for example, system security assessment, back-up, restoration, disaster recovery, change and configuration management, and reviewing of electronic data and metadata, such as audit trails and logs, for each GxP computerized systems used in the generation, processing and reporting of data.

9. Data, data transfer and data processing

- 9.1 Data may be recorded on paper or captured electronically by using equipment and instruments including those linked to computerised systems. A combination of paper and electronic formats may also be used, referred to as a “hybrid system”.
- 9.2 Data integrity consideration are also applicable to media such as photographs, videos, DVDs, imagery and thin layer chromatography plates. There should be a documented rationale for the selection of such a method.
- 9.3 Risk-reducing measures such as scribes, second person oversight, verification and checks should be implemented where there is difficulty in accurately and contemporaneously recording data related to critical process parameters or critical quality attributes.
- 9.4 Results and data sets require independent verification if deemed necessary from the DIRA or by another requirement.
- 9.5 Programmes and methods (such as processing methods in sample analysis (see also Good Chromatography Practices, TRS 1025) should ensure that data meet ALCOA+ principles. Where results or data are processed using a different method/parameters, then each version of the processing method should be recorded. Data records, content versions together with audit trails containing the required details should allow for reconstruction of all data processing in GxP computerized systems over the data life cycle.
- 9.6 Data transfer/migration procedures should include a rationale and be robustly designed and validated to ensure that data integrity is maintained during the data

life cycle. Careful consideration should be given to understanding the data format and the potential for alteration at each stage of data generation, transfer and subsequent storage. The challenges of migrating data are often underestimated, particularly regarding maintaining the full meaning of the migrated records.

Data transfer should be validated. The data should not be altered during or after it is transferred to the worksheet or other application. There should be an audit trail for this process. The appropriate quality procedures should be followed if the data transfer during the operation has not occurred correctly. Any changes in the middle layer software should be managed through the appropriate Quality Management Systems (7).

10. Good documentation practices

Note: The principles contained in this section are applicable to paper data.

- 10.1 Good documentation practices should be implemented and enforced to ensure compliance with ALCOA+ principles.
- 10.2 Data and recorded media should be durable. Ink should be indelible. Temperature-sensitive or photosensitive inks and other erasable inks should not be used. Where related risks are identified, means should be identified in order to ensure traceability of the data over their life cycle.
- 10.3 Paper should not be temperature-sensitive, photosensitive or easily oxidizable. If this is not feasible or limited, then true or certified copies should be generated.
- 10.4 Specific controls should be implemented in order to ensure the integrity of raw data and results recorded on paper records. These may include, but are not limited to:
 - control over the issuance and use of loose paper sheets at the time of recording data;
 - no use of pencil or erasers;
 - use of single-line cross-outs to record changes with the identifiable person who made the change, date and reason for the change recorded (i.e. the paper equivalent to an electronic audit trail);
 - no use of correction fluid or otherwise, obscuring the original record;
 - controlled issuance of bound, paginated notebooks;
 - controlled issuance and reconciliation of sequentially numbered copies of blank forms with authenticity controls;
 - maintaining a signature and initial record for traceability and defining the levels of signature of a record; and

- archival of records by designated personnel in secure and controlled archives.

11. Computerized systems

(Note. This section highlights some specific aspects relating to the use of computerized systems. It is not intended to repeat the information presented in the other WHO guidelines here, such as the WHO Guideline on computerized systems (3), WHO Guideline on validation (2) and WHO Guideline on good chromatography practices (7). See references.)

- 11.1 Each computerized system selected should be suitable, validated for its intended use, and maintained in a validated state.
- 11.2 Where GxP systems are used to acquire, record, transfer, store or process data, management should have appropriate knowledge of the risks that the system and users may pose to the integrity of the data.
- 11.3 Software of computerized systems, used with GxP instruments and equipment, should be appropriately configured (where required) and validated. The validation should address for example the design, implementation and maintenance of controls in order to ensure the integrity of manually and automatically acquired data; ensure that Good Documentation Practices will be implemented; and that data integrity risks will be appropriately managed throughout the data life cycle. The potential for unauthorized and adverse manipulation of data during the life cycle of the data should be mitigated and, where possible, eliminated.
- 11.4 Where electronic instruments (e.g. certain pH meters, balances and thermometers) or systems with no configurable software and no electronic data retention are used, controls should be put in place to prevent the adverse manipulation of data and to prevent repeat testing to achieve the desired result.
- 11.5 Appropriate controls for the detection of lapses in data integrity principles should be in place. Technical controls should be used whenever possible but additional procedural or administrative controls should be implemented to manage aspects of computerised system control where technical controls are missing. For example, when stand-alone computerized systems with a user-configurable output are used, Fourier-transform infrared spectroscopy (FTIR) and UV spectrophotometers have user-configurable output or reports that cannot be controlled using technical controls. Other examples of non-technical detection and prevention mechanisms may include, but are not limited to, instrument usage logbooks and electronic audit trails.

Access and privileges

- 11.6. There should be a documented system in place that defines the access and privileges of users of systems. There should be no discrepancy between paper records and electronic records where paper systems are used to request changes for the creation and inactivation of users. Inactivated users should be retained in the system. A list of active and inactivated users should be maintained throughout the system life cycle.
- 11.7. Access and privileges should be in accordance with the role and responsibility of the individual with the appropriate controls to ensure data integrity (e.g. no modification, deletion or creation of data outside the defined privilege and in accordance with the authorized procedures defining review and approval where appropriate).
- 11.8. A limited number of personnel, with no conflict of interest in data, should be appointed as system administrators. Certain privileges such as data deletion, database amendment or system configuration changes should not be assigned to administrators without justification – and such activities should only be done with documented evidence of authorization by another responsible person. Records should be maintained and audit trails should be enabled in order to track activities of system administrators. As a minimum, activity logging for such accounts and the review of logs by designated roles should be conducted in order to ensure appropriate oversight.
- 11.9. For systems generating, amending or storing GxP data, shared logins or generic user access should not be used. The computerised system design should support individual user access. Where a computerised system supports only a single user login or limited numbers of user logins and no suitable alternative computerised system is available, equivalent control should be provided by third-party software or a paper-based method that provides traceability (with version control). The suitability of alternative systems should be justified and documented (8). The use of legacy hybrid systems should be discouraged and a priority timeline for replacement should be established.

Audit trail

- 11.10 GxP systems should provide for the retention of audit trails. Audit trails should reflect, for example, users, dates, times, original data and results, changes and reasons for changes (when required to be recorded), and enabling and disenabling of audit trails.
- 11.11 All GxP relevant audit trails should be enabled when software is installed and remain enabled at all times. There should be evidence of enabling the audit

trail. There should be periodic verification to ensure that the audit trail remains enabled throughout the data life cycle.

- 11.12 Where a system cannot support ALCOA+ principles by design (e.g. legacy systems with no audit trail), mitigation measures should be taken for defined temporary periods. For example, add-on software or paper-based controls may be used. The suitability of alternative systems should be justified and documented. This should be addressed within defined timelines.

Electronic signatures

- 11.13 Each electronic signature should be appropriately controlled by, for example, senior management. An electronic signature should be:

- attributable to an individual;
- free from alteration and manipulation
- be permanently linked to their respective record; and
- date- and time-stamped.

- 11.14 An inserted image of a signature or a footnote indicating that the document has been electronically signed is not adequate unless it was created as part of the validated electronic signature process. The metadata associated with the signature should be retained.

Data backup, retention and restoration

- 11.15 Data should be retained (archived) in accordance with written policies and procedures, and in such a manner that they are protected, enduring, readily retrievable and remain readable throughout the records retention period. True copies of original records may be retained in place of the original record, where justified. Electronic data should be backed up according to written procedures.

- 11.16 Data and records, including backup data, should be kept under conditions which provide appropriate protection from deterioration. Access to such storage areas should be controlled and should be accessible only by authorized personnel.

- 11.17 Data retention periods should be defined in authorized procedures.

- 11.18 The decision for and manner in which data and records are destroyed, should be described in written procedures. Records for the destruction should be maintained.

- 11.19 Backup and restoration processes should be validated. The backup should be done routinely and periodically be restored and verified for completeness and accuracy of data and metadata. Where any discrepancies are identified, they should be investigated and appropriate action taken.

12. Data review and approval

- 12.2 There should be a documented procedure for the routine and periodic review, as well as the approval of data. Personnel with appropriate knowledge and experience should be responsible for reviewing and checking data. They should have access to original electronic data and metadata.
- 12.3 The routine review of GxP data and meta data should include audit trails. Factors such as criticality of the system (high impact versus low impact) and category of audit trail information (e.g. batch specific, administrative, system activities, and so on) should be considered when determining the frequency of the audit trail review.
- 12.4 A procedure should describe the actions to be taken where errors, discrepancies or omissions are identified in order to ensure that the appropriate corrective and preventive actions are taken.
- 12.5 Evidence of the review should be maintained.
- 12.6 A conclusion, where required, following the review of original data, metadata and audit trail records should be documented, signed and dated.

13. Corrective and preventive actions

- 13.1 Where organizations use computerized systems (e.g. for GxP data acquisition, processing, interpretation, reporting) which do not meet current GxP requirements, an action plan towards upgrading such systems should be documented and implemented in order to ensure compliance with current GxP.
- 13.2 When lapses in GxP relevant data regarding data integrity are identified, a risk-based approach may be used to determine the scope of the investigation, root cause, impact and CAPA, as appropriate. Health authorities, contract givers and other relevant organizations should be notified if the investigation identifies a significant impact or risk to, for example, materials, products, patients, reported information or data in application dossiers, and clinical trials.

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Further reading

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Appendix 1

Examples in data integrity management

This Appendix reflects on some examples in data integrity management in order to support the main text on data integrity. It should be noted that these are examples and are intended for the purpose of clarification only.

Example 1: Quality risk management and data integrity risk assessment

Risk management is an important part of good practices (GxP). Risks should be identified and assessed and controls identified and implemented in order to assist manufacturers in preventing possible DI lapses.

As an example, a Failure Mode and Effects Analysis (FMEA) model (or any other tool) can be used to identify and assess the risks relating to any system where data are, for example, acquired, processed, recorded, saved and archived. The risk assessment can be done as a prospective exercise or retrospective exercise. Corrective and preventive action (CAPA) should be identified, implemented and assessed for its effectiveness.

For example, if during the weighing of a sample, the entry of the date was not contemporaneously recorded on the worksheet but the date is available on the print-out from a weighing balance and log book for the balance for that particular activity. The fact that the date was not recorded on the worksheet may be considered a lapse in data integrity expectations. When assessing the risk relating to the lack of the date in the data, the risk may be considered different (lower) in this case as opposed to a situation when there is no other means of traceability for the activity (e.g. no print-out from the balance). When assessing the risk relating to the lapse in data integrity, the severity could be classified as “low” (the data is available on the print-out); it does not happen on a regular basis (occurrence is “low”), and it could easily be detected by the reviewer (detection is “high”) – therefore the overall risk factor may be considered low. The root cause as to why the record was not made in the analytical report at the time of weighing should still be identified and the appropriate action taken to prevent this from happening again.

Example 2: Good documentation practices in data integrity

Documentation should be managed with care. These should be appropriately designed in order to assist in eliminating erroneous entries, manipulation and human error.

Formats

Design formats to enable personnel to record or enter the correct information contemporaneously. Provision should be made for entries such as, but not limited to,

dates, times (start and finish time, where appropriate), signatures, initials, results, batch numbers and equipment identification numbers. When a computerized system is used, the system should prompt the personnel to make the entries at the appropriate step.

Blank sheets of paper

The use of blank sheets should not be encouraged. Where blank sheets are used (e.g. to supplement worksheets, laboratory notebooks and master production and control records), the appropriate controls have to be in place and may include, for example, a numbered set of blank sheets issued which are reconciled upon completion. Similarly, bound paginated notebooks, stamped or formally issued by designated personnel, allow for the detection of unofficial notebooks and any gaps in notebook pages. Authorization may include two or three signatures with dates, for example, “prepared by” or “entered by”, “reviewed by” and “approved by”.

Error in recording data

Care should be taken when entries of data and results (electronic and paper records) are made. Entries should be made in compliance with good documentation practices. Where incorrect information had been recorded, this may be corrected provided that the reason for the error is documented, the original entry remains readable and the correction is signed and dated.

Example 3: Data entry

Data entry includes for example sample receiving registration, sample analysis result recording, logbook entries, registers, batch manufacturing record entries and information in case report forms. The recording of source data on paper records should be done using indelible ink, in a way that is complete, accurate, traceable, attributable and free from errors. Direct entry into electronic records should be done by responsible and appropriately trained individuals. Entries should be traceable to an individual (in electronic records, thus having an individual user access) and traceable to the date (and time, where relevant). Where appropriate, the entry should be verified by a second person or entered through technical means such as the scanning of bar-codes, where possible, for the intended use of these data. Additional controls may include the locking of critical data entries after the data are verified and a review of audit trails for critical data to detect if they have been altered. The manual entry of data from a paper record into a computerized system should be traceable to the paper records used which are kept as original data.

Example 4: Dataset

All data should be included in the dataset unless there is a documented, justifiable, scientific explanation and procedure for the exclusion of any result or data. Whenever

out of specification or out of trend or atypical results are obtained, they should be investigated in accordance with written procedures. This includes investigating and determining CAPA for invalid runs, failures, repeats and other atypical data. The review of original electronic data should include checks of all locations where data may have been stored, including locations where voided, deleted, invalid or rejected data may have been stored. Data and metadata related to a particular test or product should be recorded together. The data should be appropriately stored in designated folders. The data should not be stored in other electronic folders or in other operating system logs. Electronic data should be archived in accordance with a standard operating procedure. It is important to ensure that associated metadata are archived with the relevant data set or securely traceable to the data set through relevant documentation. It should be possible to successfully retrieve all required data and metadata from the archives. The retrieval and verification should be done at defined intervals and in accordance with an authorized procedure.

Example 5: Legible and enduring

Data and metadata should be readable during the life cycle of the data. Electronic data are normally only legible/readable through the original software application that created it. In addition, there may be restrictions around the version of a software application that can read the data. When storing data electronically, ensure that any restrictions which may apply and the ability to read the electronic data are understood. Clarification from software vendors should be sought before performing any upgrade, or when switching to an alternative application, to ensure that data previously created will be readable.

Other risks include the fading of microfilm records, the decreasing readability of the coatings of optical media such as compact disks (CDs) and digital versatile/video disks (DVDs), and the fact that these media may become brittle.

Similarly, historical data stored on magnetic media will also become unreadable over time as a result of deterioration. Data and records should be stored in an appropriate manner, under the appropriate conditions.

Example 6: Attributable

Data should be attributable, thus being traceable to an individual and where relevant, the measurement system. In paper records, this could be done through the use of initials, full handwritten signature or a controlled personal seal. In electronic records, this could be done through the use of unique user logons that link the user to actions that create, modify or delete data; or unique electronic signatures which can be either biometric or non-biometric. An audit trail should capture user identification (ID), date and time stamps and the electronic signature should be securely and permanently linked to the signed record.

Example 7: Contemporaneous

Personnel should record data and information at the time these are generated and acquired. For example, when a sample is weighed or prepared, the weight of the sample (date, time, name of the person, balance identification number) should be recorded at that time and not before or at a later stage. In the case of electronic data, these should be automatically date- and time-stamped. In case hybrid systems are to be used, including the use for an interim period, the potential and criticality of system breaches should be covered in the assessment with documented mitigating controls in place. (The replacement of hybrid systems should be a priority with a documented CAPA plan.) The use of a scribe to record an activity on behalf of another operator should be considered only on an exceptional basis and should only take place where, for example, the act of recording places the product or activity at risk, such as, documenting line interventions by aseptic area operators. It needs to be clearly documented when a scribe has been applied.

"In these situations, the recording by the second person should be contemporaneous with the task being performed, and the records should identify both the person performing the task and the person completing the record. The person performing the task should countersign the record wherever possible, although it is accepted that this countersigning step will be retrospective. The process for supervisory (scribe) documentation completion should be described in an approved procedure that specifies the activities to which the process applies." (Extract taken from the Medicines & Healthcare Products Regulatory Agency (MHRA) GxP data integrity guidance and definitions (10).)

A record of employees indicating, their name, signature, initials or other mark or seal used should be maintained to enable traceability and to uniquely identify them and the respective action.

Example 8: Changes

When changes are made to any GxP result or data, the change should be traceable to the person who made the change as well as the date, time and reason for the change. The original value should not be obscured. In electronic systems, this traceability should be documented via computer generated audit trails or in other metadata fields or system features that meet these requirements. Where an existing computerized system lacks computer-generated audit trails, personnel may use alternative means such as procedurally controlled use of log-books, change control, record version control or other combinations of paper and electronic records to meet GxP regulatory expectations for traceability to document the what, who, when and why of an action.

Example 9: Original

The first or source capture of data or information and all subsequent data required to fully reconstruct the conduct of the GxP activity should be available. In some cases, the electronic data (electronic chromatogram acquired through high-performance liquid chromatography (HPLC)) may be the first source of data and, in other cases, the recording of the temperature on a log sheet in a room – by reading the value on a data logger. This data should be reviewed according to the criticality and risk assessment.

Example 10: Controls

Based on the outcome of risk assessment which should cover all areas of data governance and data management, appropriate and effective controls should be identified and implemented in order to assure that all data, whether in paper records or electronic records, will meet GxP requirements and ALCOA+ principles. Examples of controls may include, but are not limited to:

- the qualification, calibration and maintenance of equipment, such as balances and pH meters, that generate printouts;
- the validation of computerized systems that acquire, process, generate, maintain, distribute, store or archive electronic records;
- review and auditing of activities to ensure that these comply with applicable GxP data integrity requirements;
- the validation of systems and their interfaces to ensure that the integrity of data will remain while transferring between/among computerized systems;
- evaluation to ensure that computerized systems remain in a validated state;
- the validation of analytical procedures;
- the validation of production processes;
- a review of GxP records;
- ensuring effective review and oversight of the Batch Release Systems and processes by using different oversight and review techniques to ensure that data have not changed since the original entry; and
- the investigation of deviations, out of trend and out of specifications results.

Example 11: Accuracy

Points to consider for assuring accurate GxP records:

- the entry of critical data into a computer by an authorized person (e.g. entry of a master processing formula) requires an additional check on

the accuracy of the data entered manually. This check may be done by independent verification and release for use by a second authorized person or by validated electronic means. For example, to detect and manage risks associated with critical data, procedures would require verification by a second person;

- validation and control over formulae for calculations including electronic data capture systems;
- ensuring correct entries into the laboratory information management system (LIMS) such as fields for specification ranges;
- other critical master data, as appropriate. Once verified, these critical data fields should normally be locked in order to prevent further modification and only be modified through a formal change control process;
- the process of data transfer between systems should be validated;
- the migration of data including planned testing, control and validation; and
- when the activity is time-critical, printed records should display the date and time stamp.

4.8 General guidance on hold-time studies

Annex 4, WHO Technical Report Series, 992, 2015

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1. Introduction and background

Manufacturers should ensure that the products that they manufacture are safe, effective and of the quality required for their intended use. Systems should be in place to ensure that pharmaceutical products are produced according to validated processes and to defined procedures. Manufacturing processes should be shown to be capable of consistently manufacturing pharmaceutical products that are of the required quality and that comply with their specifications.

Good manufacturing practices (GMP) require that arrangements should be made to ensure that the dispensed raw materials and packaging materials, intermediate products, bulk and finished products are stored under appropriate conditions. Storage arrangements should not have deleterious effects on the subsequent processing, stability, safety, efficacy or quality of starting materials, intermediate products and bulk products prior to final packing. Maximum acceptable holding periods should therefore be established to ensure that intermediates and bulk product can be held, pending the next processing step, without producing results outside the acceptance criteria for the quality of the material. Normally, intermediate and bulk products should not be stored beyond the established hold time.

The choice of maximum holding period should be supported by relevant data. Studies may extend beyond the chosen maximum but it is not necessary to extend testing to determine the extreme limits at which failure occurs.

2. Glossary

Some important terms used in these guidelines are defined below. They may have different meanings in other contexts.

Bulk product. Any pharmaceutical product that has completed all processing stages up to, but not including, final packaging.

Intermediate. Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

3. Scope

These guidelines focus primarily on aspects that should be considered in the design of the hold-time studies during the manufacture of non-sterile solid dosage forms. Many of the principles described here also apply to other dosage forms such as liquids, creams and ointments. These guidelines do not cover aspects for hold times in cleaning validation, or the manufacturing of active pharmaceutical ingredients (APIs) or biologicals.

These guidelines are intended as a basic guide for use by manufacturers of pharmaceuticals and by GMP inspectors. This document is not intended to prescribe a

process for establishing hold times, but reflects aspects that should be considered in the design of the hold-time study.

Manufacturers should gather scientific and justifiable data to demonstrate that the dispensed raw materials and packaging materials, intermediate and bulk products:

- remain of appropriate quality before processing to the next stage;
- meet the acceptance criteria.

The finished product should meet the release specifications.

4. Aspects to be considered

Hold time can be considered as the established time period for which materials (dispensed raw materials, intermediates and bulk dosage form awaiting final packaging) may be held under specified conditions and will remain within the defined specifications.

Hold-time studies establish the time limits for holding the materials at different stages of production to ensure that the quality of the product does not produce results outside the acceptance criteria during the hold time. The design of the study should reflect the holding time at each stage.

Hold times should normally be determined prior to marketing of a product. The risk assessment of changes in processes, equipment, storage conditions, starting or packaging materials should include an assessment of whether further hold-time studies should be performed. Hold-time studies may be included during development on pilot-scale batches or during scale-up, and should be confirmed during process validation of commercial-scale processing (1). Further data can also be collected as part of an investigation of a deviation that occurred during manufacture.

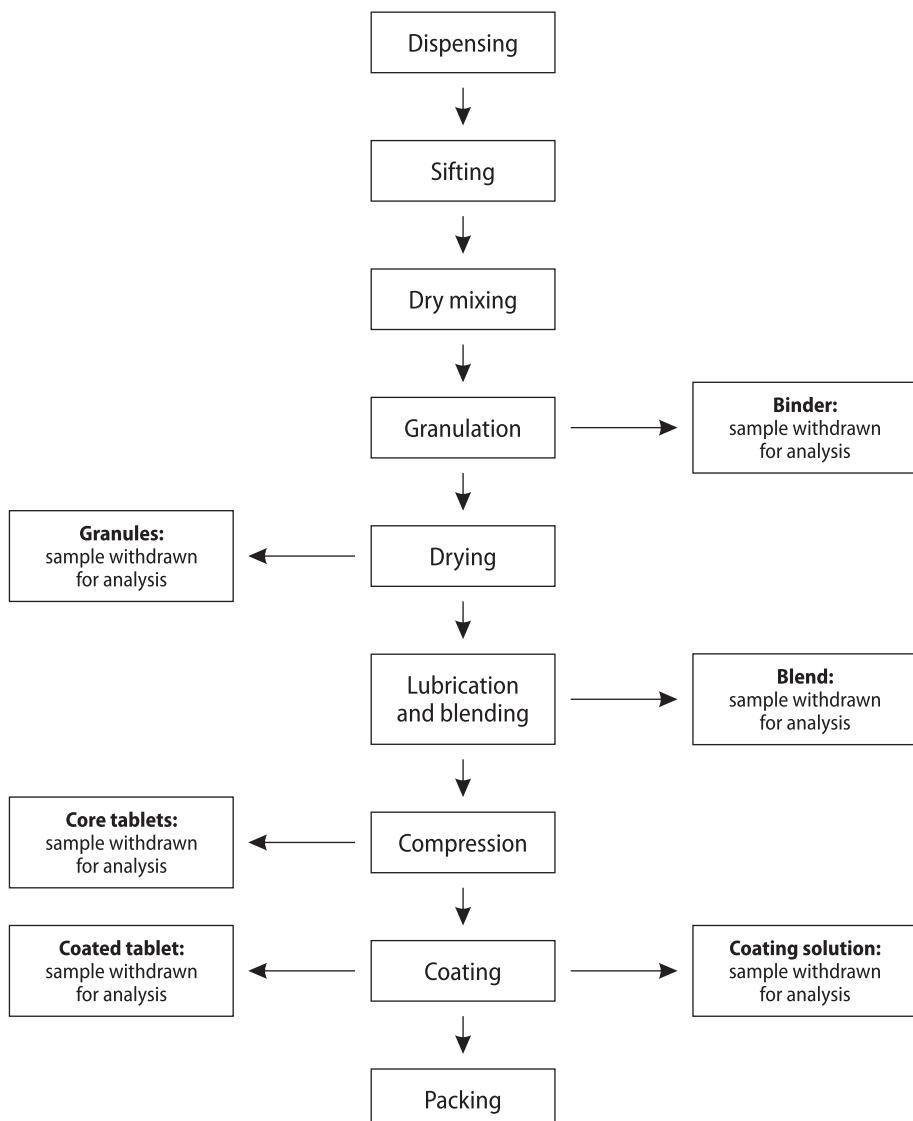
Manufacturers may use a flow chart to review the manufacturing procedure for a product and then break up the critical stages of the manufacturing process on the basis of the time period required for the particular storage and processing stages, typical pauses in the manufacturing campaign, and the potential impact of storage with reference to environmental and storage conditions. An example of a flow chart is given in Figure A4.1.

As an example, for oral tablets that are coated, the following stages may be considered:

- binder preparation to granulation – consider the granulate;
- wet granulation to drying – consider the dried granulate;
- dried granules to lubrication/blending – consider the lubricated blend;
- blend to compression;
- compression to coating – consider the tablet cores;
- coating solution to preparation – consider the coating solution;

- coating to packing – consider the bulk coated tablets;
- coating to packing in bulk;
- packing of bulk to finished packed dosage form.

Figure A4.1

Example of a flow chart for reviewing the manufacturing procedure

A written protocol, procedure or programme should be followed, which includes, for example, the activities to be performed, test parameters and acceptance criteria appropriate to the material or product under test. The protocol and report should generally include the following: a title; reference number; version; date; objective; scope; responsibility; procedure; description of the material or product; sample quantities; sampling method and criteria; acceptance limits; frequency of sampling; sampling locations; pooling of samples; storage conditions; type of container; methods of analysis; results; conclusion; recommendation; signatures; and dates. Acceptance criteria are typically more stringent than registered specifications, to provide assurance that the material is well within control. When setting the specifications, any known stability trends will need to be taken into account.

For certain products, microbiological aspects should also be considered and included where appropriate.

All testing of bulk intermediates and product should be performed using validated stability-indicating methods.

Typically one or more batches of a material, intermediate or product can be used for determining hold times. A risk-based approach can be used to determine the appropriate number of batches, considering the characteristics of the materials and other relevant aspects. A representative sample of the batch of material or product subjected to the hold-time study should be held for the defined hold period. The hold period for each category of material should be established on the basis of the study by keeping the material in either the original or simulated container used in production. The containers in which hold-time samples are stored should be the same pack as is used in production unless the pack is exceptionally large, in which case one that is equivalent (constructed of the same material and using the same closure system as the production packaging system) may be used. Reducing the size of container, when this is necessary for testing holding time, should be justified.

Where the headspace of containers used for bulk storage in manufacturing and/or quarantine is important, for example, because of a risk of potential degradation as a result of oxidation, then the hold-time studies should represent worst-case conditions. In such cases, the ratio of headspace to contents in the test containers should be at least as great as the maximum that is possible in routine production (especially taking into account part-filled containers). The environmental conditions for sample storage should be the same as those of the quarantine area/manufacture stage. A sampling plan should be established and followed for taking samples for testing at the different intervals. The amount of sample required should be calculated based on the batch size, the intervals, and the tests to be performed. Results should be compared with the initial baseline data on the control sample. Samples may be pooled for analysis where appropriate, e.g. when the analysis of a composite sample will not lead to issues that would be detectable in single samples being missed when the samples are pooled.

Where appropriate, statistical analysis of the data generated should be performed to identify trends and to justify the limits and hold time set.

Batches of finished products made from intermediates or bulk products and subjected to a hold-time study should be considered for long-term stability testing if data show adverse trending or shifting patterns during the intermediate time points up to the end of the shelf-life. The shelf-life of the product – irrespective of hold times – should be measured from the time the active ingredients are mixed with other ingredients. Normally, intermediate and bulk products should not be stored beyond the established hold time.

Table A4.1 provides examples of stages, study times and tests that may be considered for a coated tablet.

Table A4.1

Examples of stages, study times and tests that may be considered, based on risk assessment and specific product needs

Stage	Test to be carried out as per specification	Study time
Binder preparation	Microbial test, appearance, viscosity, if applicable	Initial, 2, 5, 8 hours. In case of starch: initial, 2, 5 hours
Dispersions prepared (including granulation pastes, coating solution and coating suspension)	Physical appearance, specific gravity, viscosity, sedimentation, pH, microbial test	Initial, 12, 24, 36, 48, 60, 72 hours
Granule	Description, assay, related substances, loss on drying, water content, particle size distribution, bulk density, tap density, angle of repose	Initial, 15th day, 30th day, 45th day
Blend	Microbial test, loss on drying, blend uniformity, particle size, bulk/tapped density	Initial, 15th day, 30th day, 45th day
Core tablets – uncoated (in bulk container)	Description, hardness, thickness, friability, disintegration, dissolution or dissolution profile, assay, degradation products/related substance, uniformity of dosage units, microbial test	Initial, 30th day, 45th day, 60th day and 90th day
Coated tablets (in bulk container)	Description, appearance or visual examination, hardness, thickness, friability, disintegration, dissolution or dissolution profile, assay, degradation products/related substance, moisture content, microbial test	Initial, 30th day, 45th day, 60th day and 90th day

Reference

1. Supplementary guidelines on GMP: validation, non-sterile process validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 3 (WHO Technical Report Series, No. 992; https://iris.who.int/bitstream/handle/10665/176954/9789240693968_eng.pdf?sequence=1&isAllowed=y).

4.9 Stability testing of active pharmaceutical ingredients and finished pharmaceutical products

Annex 10, WHO Technical Report Series, 1010, 2018

Introduction and background

The guidance on *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* was published as Annex 2 in the World Health Organization (WHO) Technical Report Series, No. 953, 2009 (1).

The aim of these regulatory guidelines is to outline the core stability data package required for registration of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs), replacing the previous WHO guidelines in this area. The guidelines cross-refer to the series of related documents published by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (2) and other WHO guidelines.

It was recommended that at the time of their publication these guidelines should also be applied to products that are already being marketed, making allowance for an appropriate transition period, for example, they could become applicable upon re-registration or upon re-evaluation.

The 2009 guidance not only followed the usual consultation process, but it was also the result of numerous discussions with the various regulatory forums, including ICH. As a result, the ICH parties withdrew one of their guidance texts (Q1F) and published the following text on their website:

"Explanatory Note on the Withdrawal of ICH Q1F for the ICH Website"

ICH Q1 F Stability Data Package for Registration Applications in Climatic Zones III and IV defined storage conditions for stability testing in countries located in Climatic Zones III (hot and dry) and IV (hot and humid), i.e. countries not located in the ICH regions and not covered by ICH Q1 A (R2) Stability Testing for New Drug Substances and Drug Products. ICH Q1 F described harmonised global stability testing requirements in order to facilitate access to medicines by reducing the number of different storage conditions. In the course of the discussions which led to the development of the guideline, WHO conducted a survey amongst their member states to find consensus on 30 °C/65% [relative humidity] RH as the long-term storage conditions for hot and humid regions. As no significant objections were raised in this survey, 30 °C/65% RH was defined as the long-term storage condition for Climatic Zone III/IV countries in ICH Q1F. The document was adopted by the ICH Steering Committee in February 2003 and subsequently implemented in the ICH regions.

However, based on new calculations and discussions, some countries in Climatic Zone IV have expressed their wish to include a larger safety margin for medicinal products to be marketed in their region than foreseen in ICH Q1F. As a consequence, several countries and regions have revised their own stability testing guidelines, defining up to 30 °C/75% RH as the long-term storage conditions for hot and humid regions. Due to this divergence in global stability testing requirements, the ICH Steering Committee has decided to withdraw ICH Q1F and to leave definition of storage conditions in Climatic Zones III and IV to the respective regions and WHO (<https://www.who.int/publications/m/item/trs953-annex2-appendix1>).

In assessing the impact of the withdrawal of ICH Q1F on intermediate testing conditions defined in ICH Q1A (R2), the decision was reached to retain 30 °C/65%RH. However, regulatory authorities in the ICH regions have agreed that the use of more stringent humidity conditions such as 30 °C/75% RH will be acceptable should the applicant decide to use them.”¹

Based on recent developments, an analysis was commissioned to evaluate whether the existing guidelines would need to be updated.

During the joint meeting on regulatory guidance for multisource products with the Medicines Quality Assurance Group and the Prequalification of Medicines Team assessment group held in Copenhagen from 8 to 9 July 2016, this analysis was discussed in detail and feedback provided by the participants on the report as well as on the various sections of the existing guidelines. In conclusion the participants agreed that a revision of this text would be timely.

¹ https://database.ich.org/sites/default/files/Q1F_Explanatory_Note.pdf.

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1. Introduction

1.1 Objectives of these guidelines

The aim of these guidelines is to outline the core stability data package required for registration of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs), replacing the previous WHO guidelines in this area (1). However, alternative approaches can be used when they are scientifically justified. Further guidance can be found in guidelines published by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (2), in the *WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part* (3), *WHO Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part* (4) and *WHO guidelines on the active pharmaceutical ingredient master file procedure* (5).

It is recommended that these guidelines should also be applied to products that are already being marketed, for example, upon re-registration or upon re-evaluation.

1.2 Scope of these guidelines

These guidelines apply to new and existing APIs and address information to be submitted in original and subsequent applications for marketing authorization of their related FPP for human use. These guidelines may generally apply to stability testing for biologicals; however, there are additional requirements specific to such products and further guidance can be found in ICH guideline Q5C (2).

1.3 General principles

The purpose of stability testing is to provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability testing programme also includes the study of product-related factors that influence its quality, for example, interaction of the API with excipients, container-closure systems and packaging materials. In fixed-dose combination FPPs (fixed-dose combinations (FDCs)) the interaction between two or more APIs also has to be considered.

As a result of stability testing, a retest period for the API (in exceptional cases, for example, for unstable APIs, a shelf life is given) or a shelf life for the FPP can be established and storage conditions can be recommended. An API can be considered unstable (under the conditions studied, in a particular type of packaging, etc.) when a significant change is observed.

Various analyses have been done to identify suitable testing conditions for WHO Member States based on climatic data, to enable each Member State to decide on long-term (real-time) stability testing conditions. Those Member States that have

notified WHO of the long-term stability testing conditions they require when requesting a marketing authorization are listed in “Long-term stability testing conditions as identified by WHO Member States”.²

2. Guidelines

2.1 Active pharmaceutical ingredient

2.1.1 General

Information on the stability of the API is an integral part of the systematic approach to stability evaluation. Potential attributes to be studied during stability testing of an API are listed in the examples of testing parameters (Appendix 1). **The selection of potential attributes and time points to be tested should be justified.**

The retest period or shelf life assigned to the API by the API manufacturer should be derived from stability testing data.

2.1.2 Stress testing

Stress testing of the API can help identify the likely degradation products, which in turn can help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability-indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual API and the type of FPP involved.

For an API the following approaches may be used:

- when available, it is acceptable to provide the relevant data published in the scientific literature to support the identified degradation products and pathways;
- when no published data are available, stress testing should be performed.

Stress testing may be carried out on a single batch of the API. It should include the effect of temperature (in 10 °C increments (for example, at 50 °C, 60 °C) above the temperature used for accelerated testing), humidity (for example, 75% relative humidity (RH) or greater) and, where appropriate, oxidation and photolysis of the API. The testing should also evaluate the susceptibility of the API to hydrolysis across a justified range of pH values when in solution or suspension (6).

Assessing the necessity for photostability testing should be an integral part of a stress testing strategy. More details can be found in other guidelines (2).

The objective of stress testing is to identify primary degradation products and not to completely degrade the API. The conditions studied should cause degradation

² http://www.who.int/medicines/areas/quality_safety/quality_assurance/StabilityConditionsTable2UupdatedMarch2015.pdf?ua=1, accessed 1 March 2017.

to occur to a small extent, typically 10–30% loss of API as determined by assay when compared with non-degraded API. The target should be chosen so that some degradation occurs, but not enough to generate secondary products. For this reason, the conditions and duration may need to be varied when the API is especially susceptible to a particular stress factor. In the total absence of degradation products after 10 days the API is considered stable under the particular stress condition. However, in this case the stress conditions employed should be justified.

Although examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long-term storage conditions.

Results from these studies will form an integral part of the information provided to regulatory authorities.

2.1.3 Selection of batches

The requirements that follow are not intended to apply to variations; these are covered in section 2.2.12 Variations.

Data from stability studies on at least three primary batches of the API should normally be provided. The batches should be manufactured at a minimum of pilot scale by the same synthesis route as production batches, and using a method of manufacture and a procedure that simulates the final process to be used for production batches. The overall quality of the batches of API placed on stability studies should be representative of the quality of the material to be made on a production scale.

Other supporting data can be provided.

2.1.4 Container-closure system

The stability studies should be conducted on the API packaged in a container-closure system that is the same as, or simulates, the packaging proposed for storage and distribution.

2.1.5 Specification

Stability studies should include testing of stability-indicating attributes of the API, i.e. those that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes. A guide to the potential attributes to be tested in the stability studies is provided in Appendix 1.

Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed will depend on the results from validation studies (7, 8).

2.1.6 Testing frequency

For long-term studies, the frequency of testing should be sufficient to establish the stability profile of the API.

For APIs with a proposed retest period or shelf life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year, and annually thereafter throughout the proposed retest period or shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six-month study is recommended. Where it is expected (based on development experience) that results from accelerated studies are likely to approach significant change criteria, additional testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design. When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g. 0, 6, 9 and 12 months), from a 12-month study is recommended.

2.1.7 Storage conditions

In general, an API should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage and shipment.

Storage condition tolerances are defined as the acceptable variations in temperature and RH of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in these guidelines. The storage conditions should be monitored and recorded. Short-term environmental changes due to opening the doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be assessed, addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effects assessed.

The following requirements for data at the time of submission are not generally intended to apply to variations; instead see section 2.2.12 Variations. For new APIs, the long-term testing should normally have taken place over a minimum of 12 months for the number of batches specified in section 2.1.3 at the time of submission, and should be continued for a period of time sufficient to cover the proposed retest period or shelf life. For existing APIs, data covering a minimum of six months may be submitted. Additional data accumulated during the period while the registration application is being assessed should be submitted to the authorities when submitting data in response to outstanding questions. Data from the accelerated storage condition and, if appropriate, from

the intermediate storage condition, can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated and, where appropriate, intermediate storage conditions for APIs are detailed in sections 2.1.7.1–2.1.7.3. The general case applies if the API is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

If long-term studies are conducted at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{RH} \pm 5\% \text{RH}$ and “significant change” occurs at any time during six months’ testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. In this case, testing at the intermediate storage condition should include all long-term tests, unless otherwise justified, and the initial application should include a minimum of six months’ data from a 12-month study at the intermediate storage condition.

“Significant change” for an API is defined as failure to meet its specification.

2.1.7.1 General case

Study	Storage condition	Minimum time period covered by data at submission
Long-term ^a	$25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{RH} \pm 5\% \text{RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\% \text{RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\% \text{RH}$	12 months or 6 months as described in point 2.1.7
Intermediate ^b	$30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\% \text{RH}$	6 months
Accelerated	$40^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\% \text{RH}$	6 months

^a Whether long-term stability studies are performed at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{RH} \pm 5\% \text{RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\% \text{RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\% \text{RH}$ is determined by the climatic condition under which the API is intended to be stored (see “Long-term stability testing conditions as identified by WHO Member States”). Testing at a more severe long-term condition can be an alternative to testing condition, i.e. $25^{\circ}\text{C}/60\% \text{RH}$ or $30^{\circ}\text{C}/65\% \text{RH}$ for zone II.

^b If $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/65\% \text{RH} \pm 5\% \text{RH}$ or $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{RH} \pm 5\% \text{RH}$ is the long-term condition there is no intermediate condition.

2.1.7.2 Active pharmaceutical ingredients intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long-term	$5^{\circ}\text{C} \pm 3^{\circ}\text{C}$	12 months or 6 months as referred to in section 2.1.7

Table *continued*

Study	Storage condition	Minimum time period covered by data at submission
Accelerated ^a	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 months

^a Whether accelerated stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to storage testing at 25 °C/60% RH or 30 °C/65% RH.

Data on refrigerated storage should be assessed according to the evaluation section of these guidelines, except where explicitly noted below.

If significant change occurs between three and six months' testing at the accelerated storage condition, the proposed retest period should be based on the data available at the long-term storage condition.

If significant change occurs within the first three months' testing at the accelerated storage condition a discussion should be provided addressing the effect of short-term excursions outside the label storage condition, e.g. during shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the API for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test an API for the whole six months when a significant change has occurred within the first three months.

2.1.7.3 Active pharmaceutical ingredients intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long-term	–20 °C ± 5 °C	12 months or 6 months as referred to in section 2.1.7

In the rare case of any API of nonbiological origin being intended for storage in a freezer, the retest period or shelf life should be based on the long-term data obtained at the long-term storage condition. In the absence of an accelerated storage condition for APIs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. 5 °C ± 3 °C or 25 °C ± 2 °C or 30 °C ± 2 °C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition, e.g. during shipping or handling.

2.1.7.4 Active pharmaceutical ingredients intended for storage below –20 °C

APIs intended for storage below –20 °C should be treated on a case-by-case basis.

2.1.8 Stability commitments

When the available long-term stability data on primary batches do not cover the proposed retest period or shelf life granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the retest period or shelf life.

Where the submission includes long-term stability data on three production batches covering the proposed retest period or shelf life, a post-approval commitment is considered unnecessary. Otherwise one of the following commitments should be made:

- if the submission includes data from stability studies on three production batches, a commitment should be made to continue these studies through the proposed retest period or shelf life;
- if the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed retest period and to place additional production batches, up to a total of at least three, in long-term stability studies through the proposed retest period or shelf life;
- if the submission does not include stability data on production batches, a commitment should be made to place the first three production batches (see section 2.1.3) on long-term stability studies through the proposed retest period or shelf life.

The stability protocol used for long-term studies for the stability commitment should be the same as that for the primary batches, unless otherwise scientifically justified.

See also 2.1.11 Ongoing stability studies.

2.1.9 Evaluation

The primary stability programme should be described in a written protocol and the results presented in a formal report as outlined in 2.1.11.

The purpose of the stability study is to establish – based on testing a minimum of three batches of the API, unless otherwise justified, and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological and microbiological tests) – a retest period or shelf life applicable to all future batches of the API manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned retest period or shelf life.

The data may show so little degradation and so little variability that it is apparent from looking at them that the requested retest period or shelf life will be granted. Under these circumstances it is normally unnecessary to go through the statistical analysis.

One approach for analysing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g. P values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall retest period or shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. As far as possible the choice of model should be justified by a physical and/or chemical rationale and should also take into account the amount of available data (parsimony principle to ensure a robust prediction). Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the long-term data from the long-term storage condition beyond the observed range to extend the retest period or shelf life can be undertaken if justified. This justification should be based on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size and existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data (please refer to ICH Q1E).

Any evaluation should cover not only the assay but also the levels of degradation products and other stability-indicating attributes.

2.1.10 Statements and labelling

A storage statement should be established for display on the label based on the stability evaluation of the API. Where applicable, specific instructions should be provided, particularly for APIs that cannot tolerate freezing or excursions in temperature. Terms such as “ambient conditions” or “room temperature” should be avoided.

The recommended labelling statements for use when supported by the stability studies are provided in Appendix 2.

A retest period should be derived from the stability information, and a retest date should be displayed on the container label if appropriate.

After this retest period a batch of API destined for use in the manufacture of an FPP could be retested and then, if in compliance with the specification, could be used

immediately (e.g. within 30 days). If retested and found compliant, the batch does not receive an additional period corresponding to the time established for the retest period. However, an API batch can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For APIs known to be labile (e.g. certain antibiotics) it is more appropriate to establish a shelf life than a retest period.

2.1.11 Ongoing stability studies

The stability of the API should be monitored according to a continuous and appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products). The purpose of the ongoing stability programme is to monitor the API and to determine that the API remains, and can be expected to remain, within specifications under the storage conditions indicated on the label, within the retest period or shelf life in all future batches.

The ongoing stability programme should be described in a written protocol and the results presented in a formal report that should be available on site.

The protocol for an ongoing stability programme should extend to the end of the retest period or shelf life and should include, but not be limited to, the following parameters:

- number of batch(es) and different batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test parameters with acceptance criteria or reference to the attached specifications;
- reference to test methods;
- description of the container-closure system(s);
- testing frequency;
- description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines, and consistent with the API labelling, should be used);
- other applicable parameters specific to the API.

At least one production batch per year of API (unless none is produced during that year) should be added to the stability monitoring programme and generally should be tested at least every 6 months in the first year and then annually to confirm the stability (7).

In certain situations additional batches should be included in the stability programme and may require more frequent testing. For example, a stability study should be initiated after any significant change or significant deviation of the synthetic route, process or container-closure system that may have an impact upon the stability of the API (refer to section 2.2.12 Variations).

Out-of-specification (OOS) results or significant atypical trends should be investigated. Any confirmed significant change or OOS result should be reported immediately to the relevant finished product manufacturer. The possible impact on batches on the market should be considered in consultation with the relevant finished product manufacturers and the competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained and should be available on site. This summary should be subjected to periodic review.

2.2 Finished pharmaceutical product

2.2.1 General

The design of the stability studies for the FPP should be based on knowledge of the behaviour and properties of the API, information from stability studies on the API and on experience gained from preformulation studies, similar marketed formulations and investigational FPPs. The likely changes during storage and the rationale for the selection of attributes to be tested in the stability studies should be stated.

2.2.2 Stress testing

Photostability testing, which is an integral part of stress testing, should be conducted on at least one primary batch of the FPP if appropriate. More details can be found in other guidelines (2).

Additional stress testing of specific types of dosage forms may be appropriate, e.g. cyclic studies for semi-solid products or freeze-thaw studies for liquid products.

2.2.3 Selection of batches

The requirements that follow are not generally intended to apply to variations, which are covered in section 2.2.12 Variations.

For FPPs containing new APIs, data from stability studies should be provided on at least three primary batches of each proposed strength of the FPP. Two of the three batches should be at least pilot-scale batches and the third batch can be smaller, if justified (see example below).

For FPPs containing existing APIs (e.g. generics), data should be provided on not less than two batches of at least pilot scale, or in the case of an uncomplicated³ FPP (e.g. immediate-release solid FPPs (with noted exceptions) or non-sterile solutions), at least one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP.

³ The term "complicated FPP" includes sterile products, metered dose inhaler products, dry powder inhaler products and transdermal delivery systems. Solid oral products considered "complicated" include modified-release FPPs, products containing problematical APIs such as ritonavir and FDCs containing APIs such as rifampicin or artemisinin.

The primary batches should be of the same formulation and packaged in the same container-closure system as that proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing.

When a batch size smaller than pilot scale is used as a primary batch, data or a discussion is required to confirm that the smaller batch is representative of the intended production size, including its formulation and method of manufacture.

Where possible, batches of the FPP should be manufactured using different batches of the API(s).

Stability studies should be performed on each individual strength, dosage form and container type and size of the FPP unless bracketing or matrixing is applied (refer to ICH Q1D).

2.2.4 Container-closure system

Stability testing should be conducted on the dosage form packaged in the primary container-closure systems proposed for marketing. If the secondary container-closure system has protective properties, and labelling clearly indicates that the product is to be stored in the primary and secondary packaging (e.g. “store tablets in blisters in the provided cartons”), or if the product is packaged in a semi-permeable container where components from the secondary packaging can migrate into the product, the secondary packaging may also form part of the packaging system for stability samples. Any available studies carried out on the FPP outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

2.2.5 Specification

Stability studies should include testing of stability-indicating attributes of the FPP, i.e. those that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes, preservative content (e.g. antioxidant or antimicrobial preservatives) and functionality tests (e.g. for a dose delivery system). Examples of testing parameters in the stability studies are listed in Appendix 1. Analytical procedures should be fully validated and stability-indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf-life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf-life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf-life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated

during development of the pharmaceutical product with the product in its final formulation (except for preservative concentration) intended for marketing. A single primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

2.2.6 Testing frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the FPP.

For products with a proposed shelf life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year and annually thereafter throughout the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, testing should be increased either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g. 0, 6, 9 and 12 months), from a 12-month study is recommended.

The initial date of storage should be considered t0 and stability time points should be defined as a date with respect to t0. For example, if t0 is 1 January 2020 then the one-month time point corresponds to either 1 February or 31 January 2020. For each time point, samples should be withdrawn and tested as per the protocol. Testing should be completed as soon as possible. Deviations from the protocol should be recorded and justified.

Reduced designs, i.e. matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified (refer to ICH Q1D).

2.2.7 Storage conditions

Stability data must demonstrate stability of the medicinal product throughout its intended shelf life under the climatic conditions prevalent in the target countries. Merely applying the same requirements appropriate to other markets could potentially lead to substandard products if stability studies are conducted at the storage conditions for countries in Climatic Zone I/II when the products are supplied in countries in Climatic Zones III and IV.

In general an FPP should be evaluated under storage conditions with specified tolerances that test its thermal stability and, if applicable, its sensitivity to moisture

or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment and subsequent use with due regard to the climatic conditions in which the product is intended to be marketed.

The orientation of the product during storage, i.e. upright, on the side or inverted, as well as the rationale for the orientation, may need to be included in a protocol where contact of the product with the closure system may be expected to affect the stability of the products contained (e.g. liquids and semisolids), or where there has been a change in the container-closure system.

Storage condition tolerances are usually defined as the acceptable variations in temperature and RH of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in these guidelines. The storage conditions should be monitored and recorded. Short-term environmental changes due to opening of the doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be assessed, addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effects assessed.

The following requirements for data at the time of submission are not generally intended to apply to variations; instead refer to section 2.2.12 Variations. At the time of submission, the long-term testing should cover a minimum of six months for FPPs containing existing APIs or 12 months for FPPs containing new APIs and should be continued for a period of time sufficient to cover the proposed shelf life. The period of data collection required at the time of submission may be shortened in some circumstances, for example, to address shortages of medicines.

Additional data accumulated during the assessment period of the registration application should be submitted to the authorities when submitting data in response to outstanding questions. Data from the accelerated storage condition and from the intermediate conditions, where appropriate, can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated and, where appropriate, intermediate storage conditions for FPPs are detailed in the sections below. The general case applies if the FPP is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

2.2.7.1 General case

Study	Storage condition	Minimum time period covered by data at submission
Long-term ^a	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12 months or 6 months as described in point 2.2.7

Table *continued*

Study	Storage condition	Minimum time period covered by data at submission
Intermediate ^b	30 °C ± 2 °C/65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

^a Whether long-term stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is determined by the climatic zone in which the FPP is intended to be marketed. Testing at a more severe long-term condition can be an alternative to storage at 25 °C/60% RH or 30 °C/65% RH.

^b If 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25 °C ± 2 °C/60% RH ± 5% RH and “significant change” occurs at any time during 6 months’ testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. In this case the initial application should include a minimum of six months’ data from a 12-month study at the intermediate storage condition.

In general, “significant change” for an FPP is defined as:

- a change from the initial content of API(s) of 5% or more detected by assay, or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
- any degradation product exceeding its acceptance criterion;
- failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g. colour, phase separation, resuspendability, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams, partial loss of adhesion for transdermal products) may be expected under accelerated conditions.

Also, as appropriate for the dosage form:

- failure to meet the acceptance criterion for pH; or
- failure to meet the acceptance criteria for dissolution for 12 dosage units.

2.2.7.2 FPPs packaged in impermeable containers

Parameters required to classify the packaging materials as permeable or impermeable depend on the characteristics of the packaging material, such as sealing, thickness and permeability coefficient. The suitability of the packaging material used for a particular

product is determined by its product characteristics. Containers generally considered to be moisture-impermeable include glass ampoules.

Sensitivity to moisture or potential for solvent loss is not a concern for FPPs packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus stability studies for products stored in impermeable containers can be conducted under any controlled or ambient RH condition.

2.2.7.3 FPPs packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological and microbiological stability. This evaluation can be carried out under conditions of low RH, as discussed below. Ultimately it should be demonstrated that aqueous-based FPPs stored in semi-permeable containers could withstand environments with low RH.

Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Study	Storage condition	Minimum time period covered by data at submission
Long-term ^a	25 °C ± 2 °C/40% RH ± 5% RH or 30 °C ± 2 °C/35% RH ± 5% RH	12 months or 6 months as described in point 2.2.7
Intermediate ^b	30 °C ± 2 °C/35% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/not more than (NMT) 25% RH	6 months

^a Whether long-term stability studies are performed at 25 °C ± 2 °C/40% RH ± 5% RH or 30 °C ± 2 °C/35% RH ± 5% RH is determined by the climatic condition under which the FPP is intended to be marketed. Testing at 30 °C/35% RH can be an alternative to the storage condition at 25 °C/40% RH.

^b If 30 °C ± 2 °C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

Products meeting the specifications when stored under the accelerated conditions and the long-term storage conditions appropriate to the intended market, as specified in the table above, have demonstrated the integrity of the packaging in semi-permeable containers. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate that the pharmaceutical product would not have significant water loss throughout the proposed shelf life if stored at 25 °C/40% RH or 30 °C/35% RH.

For long-term studies conducted at 25 °C ± 2 °C/40% RH ± 5% RH, that fail the accelerated testing with regard to water loss and show significant change with respect to any other parameters, additional testing at the “intermediate” storage condition should be performed as described under the general case to evaluate the temperature effect at 30 °C.

A 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of three months' storage at 40 °C and not more than (NMT) 25% RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5% or more after an equivalent of three months' storage at 40 °C/NMT 25% RH may be appropriate, if justified.

An alternative approach to studies at the low RH as recommended in the table above (for either long-term or accelerated testing) is to perform the stability studies under higher RH and to derive the water loss at the low RH through calculation. This can be achieved by experimentally determining the permeation coefficient for the container-closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container-closure system can be experimentally determined by using the worst-case scenario (e.g. the most diluted of a series of concentrations) for the proposed FPP.

Example of an approach for determining water loss

For a product in a given container-closure system, container size and fill, an appropriate approach for deriving the rate of water loss at the low RH is to multiply the rate of water loss measured at an alternative RH at the same temperature, by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative RH over the storage period should be demonstrated.

For example, at a given temperature, e.g. 40 °C, the calculated rate of water loss during storage at NMT 25% RH is the rate of water loss measured at 75% RH multiplied by 3.0, the corresponding water loss rate ratio.

Low-humidity testing conditions	Alternative testing condition	Ratio of water loss rates	Calculation
25 °C/40% RH	25 °C/60% RH	1.5	(100–40)/(100–60)
30 °C/35% RH	30 °C/65% RH	1.9	(100–35)/(100–65)
30 °C/35% RH	30 °C/75% RH	2.6	(100–35)/(100–75)
40 °C/NMT 25% RH	40 °C/75% RH	3.0	(100–25)/(100–75)

Valid water loss rate ratios at RH conditions other than those shown in the table above can also be used.

2.2.7.4 FPPs intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long-term	$5\text{ }^\circ\text{C} \pm 3\text{ }^\circ\text{C}$	12 months or 6 months as referred to in section 2.2.7
Accelerated ^a	$25\text{ }^\circ\text{C} \pm 2\text{ }^\circ\text{C}/60\%$ RH $\pm 5\%$ RH or $30\text{ }^\circ\text{C} \pm 2\text{ }^\circ\text{C}/65\%$ RH $\pm 5\%$ RH or $30\text{ }^\circ\text{C} \pm 2\text{ }^\circ\text{C}/75\%$ RH $\pm 5\%$ RH	6 months

^a Whether accelerated stability studies are performed at $25\text{ }^\circ\text{C} \pm 2\text{ }^\circ\text{C}/60\%$ RH $\pm 5\%$ RH or $30\text{ }^\circ\text{C} \pm 2\text{ }^\circ\text{C}/65\%$ RH $\pm 5\%$ RH or $30\text{ }^\circ\text{C} \pm 2\text{ }^\circ\text{C}/75\%$ RH $\pm 5\%$ RH is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to the storage condition at $25\text{ }^\circ\text{C}/60\%$ RH or $30\text{ }^\circ\text{C}/65\%$ RH.

If the FPP is packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss.

Data from refrigerated storage should be assessed according to the evaluation section of these guidelines, except where explicitly noted below.

If significant change occurs between three and six months' testing at the accelerated storage condition, the proposed shelf life should be based on the data available from the long-term storage condition.

If significant change occurs within the first three months' testing at the accelerated storage condition, a discussion should be provided addressing the effect of short-term excursions outside the label storage condition, e.g. during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the FPP for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test a product throughout six months when a significant change has occurred within the first three months of accelerated studies at the specific condition chosen in accordance with the risk analysis.

2.2.7.5 FPPs intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long-term	$-20\text{ }^\circ\text{C} \pm 5\text{ }^\circ\text{C}$	12 months or 6 months as referred to in section 2.2.7

For FPPs intended for storage in a freezer, the shelf life should be based on the long-term data obtained at the long-term storage condition. In the absence of an

accelerated storage condition for FPPs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. $5\text{ }^{\circ}\text{C} \pm 3\text{ }^{\circ}\text{C}$ or $25\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ or $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition.

2.2.7.6 FPPs intended for storage below $-20\text{ }^{\circ}\text{C}$

FPPs intended for storage at temperatures below $-20\text{ }^{\circ}\text{C}$ should be treated on a case-by-case basis.

2.2.8 Stability commitments

One or more of the following commitments should be made.

- When the available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post-approval throughout the proposed shelf life. This is the primary batch stability commitment.
- If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to place the next production batches, up to a total of at least three, on long-term stability studies throughout the proposed shelf life and on accelerated studies for six months. This is the production batch stability commitment.
- For each product, an ongoing stability programme is required to monitor the product over its shelf life and to determine that the product remains and can be expected to remain within specifications under the storage conditions on the label. See 2.2.13. This is the ongoing stability commitment.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

2.2.9 Evaluation

The primary stability programme should be described in a written protocol and the results presented in a formal report as outlined in 2.2.13.

A systematic approach should be adopted to the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological and microbiological tests, including particular attributes of the dosage form (e.g. dissolution rate for solid oral dosage forms). *Where appropriate, a summary of additional knowledge and an understanding of stability gained from supporting studies, modelling, predictive tools, etc., may be incorporated to support knowledge gained from the primary stability programme.*

The purpose of the stability study is to establish, based on testing a minimum number of batches of the FPP as specified in section 2.2.3, a shelf life and label storage instructions applicable to all future batches of the FPP manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the statistical analysis.

One approach for analysing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g. P values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. As far as possible, the choice of model should be justified by a physical and/or chemical rationale and should also take into account the amount of available data (parsimony principle to ensure a robust prediction).

Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the long-term data from the long-term storage condition beyond the observed range to extend the shelf life can be undertaken, if justified. This justification should be based on what is known about the mechanisms of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size and the existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data (refer to ICH Q1E).

Any evaluation should consider not only the assay but also the degradation products and other appropriate attributes.

2.2.10 Statements and labelling

A storage statement should be established for the label based on the stability evaluation of the FPP. Where applicable, specific instructions should be provided, particularly for FPPs that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” should be avoided.

There should be a direct link between the storage statement on the label and the demonstrated stability of the FPP. An expiry date should be displayed on the container label.

The labelling statements recommended for use, if supported by the stability studies, are provided in Appendix 2. Information on the interpretation and conversion of storage statements for products approved in zone II when the products are to be distributed in zone IV is provided in Appendix 3.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Additional labelling statements could be used in cases where the results of the stability testing demonstrate limiting factors (see Appendix 2).

2.2.11 In-use and hold time stability

The purpose of in-use stability testing is to provide information for the labelling on the preparation, storage conditions and utilization period of multidose products after opening, reconstitution or dilution of a solution. Examples include an antibiotic injection supplied as a powder for reconstitution, or a moisture-sensitive or hygroscopic solid oral FPP in a large format multidose container (e.g. high density polyethylene (HDPE) bottle of 500 tablets). In general, a 30-day in-use period is normally considered acceptable without further supporting data.

As far as possible the test should be designed to simulate the use of the FPP in practice, taking into consideration the filling volume of the container and any dilution or reconstitution before use. At intervals comparable to those that occur in practice, appropriate quantities should be removed by the withdrawal methods normally used and described in the product literature.

The physical, chemical and microbial properties of the FPP that are susceptible to change during storage should be determined over the period of the proposed in-use shelf life. If possible, testing should be performed at intermediate time points and at the end of the proposed in-use shelf life on the final amount of the FPP remaining in the container. Specific parameters, e.g. for liquids and semisolids: the content and effectiveness of preservatives need to be studied.

A minimum of two batches, at least pilot-scale (with the exceptions outlined in 2.2.3), should be subjected to the test. At least one of these batches should be chosen towards the end of its shelf life. If such results are not available, one batch should be tested at the final point of the submitted stability studies.

This testing should be performed on primary batches of the reconstituted or diluted FPP or the solid oral FPP (as above), throughout the proposed in-use period as part of the stability studies at the initial and final time points and, if long-term data covering the shelf life are not available at the time of submission, at 12 months or the last time point at which data will be available.

In general this testing need not be repeated on commitment batches (see 2.2.8).

Consideration should also be given to hold-time studies of bulk products, e.g. coated tablets prior to final packaging. For example, when the bulk product may be stored for a period exceeding 30 days before being packaged and/or shipped from a manufacturing site to a packaging site, the stability of the bulk product in the intended bulk container should be evaluated and studied. Similar considerations should apply to intermediates that are stored and used for periods exceeding 30 days. Further guidance can be found in the WHO *General guidance on hold-time studies* (9).

2.2.12 Variations

Once the FPP has been registered, additional stability studies are required whenever variations are made that may affect the stability of the API or FPP. The applicant should investigate whether or not the intended change will have an impact on the quality characteristics of APIs and/or FPPs and consequently on their stability. The scope and design of the stability studies for variations are based on the knowledge and experience acquired on APIs and FPPs.

The available variation guidelines should be consulted for guidance on the expectations regarding stability requirements to support changes to the API and FPP. Note that the requirements of the guidelines of the specific regulatory authority or region prevail for a given region; however, in the absence of such guidelines, the WHO Prequalification Team: Medicines guidelines can be applied (10). Depending on the variation, either the results of a stability study or a commitment to conduct such a study is required. Variation guidelines are specific detailed guidelines, therefore the following are general categories and the guidelines should be referred to for the exact circumstances and requirements. In the aforementioned guidance document (10), changes requiring supporting data include certain changes to the API retest period or storage conditions, and to the FPP formulation, manufacturing process, container-closure system, shelf life, in-use period and storage conditions. Other changes, such as certain changes to the API certificate of suitability, certificate of prequalification, manufacturing site or manufacturing process, or certain changes to the FPP manufacturing site, batch size or container-closure system, require a commitment for stability studies to support the variations.

The results of these stability studies should be communicated to the regulatory authorities concerned, following the applicable requirements stipulated in the variation guidelines for the region.

2.2.13 Ongoing stability studies

After a marketing authorization has been granted, the stability of the FPP should be appropriately monitored according to a continuous programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products or dissolution profile) associated with the formulation in the container-closure system in

which it is marketed. The purpose of the ongoing stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the storage conditions on the label. The ongoing stability programme should be described in a written protocol and results formalized as a report.

The protocol for an ongoing stability programme should extend to the end of the shelf-life period and should include, but not be limited to, the following parameters:

- number of batch(es) per strength and different batch sizes, if applicable. The batch size should be recorded, if batch sizes differ;
- relevant physical, chemical, microbiological and biological test parameters with acceptance criteria or reference to the attached specifications;
- reference to test methods;
- description of the container-closure system(s);
- testing frequency (generally at 6 months and annual time points is sufficient for ongoing studies);
- description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines, and consistent with the product labelling, should be used); and
- other applicable parameters specific to the FPP.

The protocol for the ongoing stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorization dossier provided that this is justified and documented in the protocol (for example, the frequency of testing as above, or when updating to meet revised recommendations).

The number of batches and frequency of testing should provide sufficient data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none is produced during that year). The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol (refer to ICH Q1D).

In certain situations additional batches should be included in the ongoing stability programme. For example, an ongoing stability study should be conducted after any significant change or significant deviation to the process or container-closure system. Any reworking, reprocessing or recovery operation should also be considered for inclusion. Refer to section 2.2.12 for further details.

OOS results or significant atypical trends should be investigated. Any confirmed significant change or OOS result should be reported immediately to the relevant competent authorities. The possible impact on batches on the market should be considered in consultation with the relevant competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

3. Glossary

The definitions provided below apply to the words and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents. The following definitions are provided to facilitate interpretation of the guidelines. The definitions are consistent with those published in other WHO quality assurance guidelines. The Quality Assurance of Medicines Terminology Database was established in August 2005 and includes the definitions of terms related to quality assurance of medicines. This database is intended to help harmonize terminology and to avoid misunderstandings that may result from the different terms and their interpretations used in various WHO publications. The main publications used as a source of information to create the Quality Assurance of Medicines Terminology Database are the quality assurance guidelines included in the thirty-sixth and subsequent reports of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

accelerated testing. Studies designed to increase the rate of chemical degradation and physical change of an active pharmaceutical ingredient or finished pharmaceutical product by using exaggerated storage conditions as part of the stability testing programme. The data thus obtained, in addition to those derived from long-term stability studies, may be used to assess longer-term chemical effects under non-accelerated conditions and to evaluate the impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes.

active pharmaceutical ingredient. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

batch. A defined quantity of starting material, packaging material or finished pharmaceutical product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

bracketing. The design of a stability schedule such that only samples at the extremes of certain design factors, e.g. strength and package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g. for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container-closure system (refer to ICH Q1D).

climatic zone. The zones into which the world is divided based on the prevailing annual climatic conditions (see reference to the living document “Long-term stability testing conditions as identified by WHO Member States”⁴).

commitment batches. Production batches of an active pharmaceutical ingredient or finished pharmaceutical product for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.

container-closure system. The sum of packaging components that together contains and protects the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the finished pharmaceutical product. A packaging system is equivalent to a container-closure system.

dosage form. The form of the finished pharmaceutical product, e.g. tablet, capsule, elixir or suppository.

excipient. A substance or compound, other than the active pharmaceutical ingredient and packaging materials, that is intended or designated to be used in the manufacture of a finished pharmaceutical product.

existing active pharmaceutical ingredient. An active pharmaceutical ingredient that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority or by the World Health Organization, but requires the filing of a dossier. This would include, for example, new product dossiers and variations to multisource products.

expiry date. The date given on the individual container (usually on the label) of a product up to and including which the active pharmaceutical ingredient and finished pharmaceutical product are expected to remain within specifications if stored under the long-term conditions at which stability was established. It is set for each batch by adding the shelf life to the date of manufacture.

finished pharmaceutical product. A product that has undergone all stages of production, including packaging in its final container and labelling. A finished pharmaceutical product may contain one or more active pharmaceutical ingredients.

⁴ http://www.who.int/medicines/areas/quality_safety/quality_assurance/StabilityConditionsTable2UupdatedMarch2015.pdf?ua=1, accessed 1 March 2017.

impermeable containers. Containers that provide a permanent barrier to the passage of gases or solvents, e.g. sealed aluminium tubes for semisolids, sealed glass ampoules for solutions and aluminium/aluminium blisters for solid dosage forms (refer to 2.2.7.2).

in-use period. A period of time during which a reconstituted preparation of the finished dosage form in a multidose container, or a moisture-sensitive product in a large-format final container (e.g. high-density polyethylene (HDPE) bottles of 500) can be used after opening.

long-term stability studies. Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of an active pharmaceutical ingredient or finished pharmaceutical product, during and beyond the expected shelf life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the retest period or the shelf life, to confirm the projected retest period and shelf life, and to recommend storage conditions.

matrixing. The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same finished pharmaceutical product should be identified as, for example, covering different batches, different strengths, different sizes of the same container-closure system, and, possibly in some cases, different container-closure systems (refer to ICH Q1D).

new active pharmaceutical ingredient. Active pharmaceutical ingredient that has not been previously authorized as a medicine for use in humans in the country in question.

ongoing stability study. The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf life) of the active pharmaceutical ingredient, or confirm or extend the shelf life of the finished pharmaceutical product.

pilot-scale batch. A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger, unless otherwise adequately justified.

primary batch. A batch of an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP) used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf life, as the case may be. Primary batch requirements are outlined in 2.1.3 and 2.2.3 for the API and FPP, respectively.

production batch. A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured at production scale by using production equipment in a production facility as specified in the application.

provisional shelf life. A provisional expiry date that is based on acceptable accelerated and available long-term data for the finished pharmaceutical product to be marketed in the proposed container-closure system.

release specification. The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of an active pharmaceutical ingredient or finished pharmaceutical product at the time of its release.

retest date. The date after which an active pharmaceutical ingredient should be re-examined to ensure that the material is still in compliance with the specification and thus is still suitable for use in the manufacture of a finished pharmaceutical product.

retest period. The period of time during which the active pharmaceutical ingredient (API) is expected to remain within its specification and, therefore, can be used in the manufacture of a given finished pharmaceutical product (FPP), provided that the API has been stored under the defined conditions. After this period, a batch of API destined for use in the manufacture of an FPP should be retested for compliance with the specification and then used immediately. A batch of API can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For most substances known to be labile, it is more appropriate to establish a shelf life than a retest period. The same may be true for certain antibiotics.

semi-permeable containers. Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by adsorption onto one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient. Examples of semi-permeable containers include plastic bags and semi-rigid, low-density polyethylene (LDPE) pouches for large-volume parenterals and LDPE and high-density polyethylene (HDPE) ampoules, bottles and vials.

shelf life. The period of time during which an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP), if stored under the conditions in which stability was established, is expected to comply with the specification as determined by stability studies on a number of batches of the API or FPP. The shelf life is used to establish the expiry date of each batch.

shelf-life specification. The combination of physical, chemical, biological and microbiological tests and acceptance criteria that an active pharmaceutical ingredient or finished pharmaceutical product should meet throughout its retest period or shelf life.

significant change. (See sections 2.1.7 and 2.2.7.)

“Significant change” for an active pharmaceutical ingredient (API) is defined as failure to meet its specification. In general “significant change” for a finished

pharmaceutical product is defined as: a 5% or more change in assay from its initial content of API(s), or failure to meet the acceptance criteria for potency when using biological or immunological procedures.

Any degradation product exceeding its acceptance criterion.

1. Failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g. colour, phase separation, resuspendability, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams or partial loss of adhesion for transdermal products) may be expected under accelerated conditions.

Also, as appropriate for the dosage form:

2. failure to meet the acceptance criterion for pH; or
3. failure to meet the acceptance criteria for dissolution for 12 dosage units.

specification. A list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges or other criteria for the tests described. It establishes the set of criteria to which an active pharmaceutical ingredient or finished pharmaceutical product should conform to be considered acceptable for its intended use. See *Release specification* and *Shelf-life specification*.

stability-indicating methods. Validated analytical procedures that can detect the changes with time in the chemical, physical or microbiological properties of the active pharmaceutical ingredient (API) or finished pharmaceutical product, and that are specific so that the content of the API, degradation products and other components of interest can be accurately measured without interference.

stability studies (stability testing). Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the retest period (or shelf life) of an active pharmaceutical ingredient or the shelf life of a finished pharmaceutical product.

stress testing (of the active pharmaceutical ingredient (API)). Studies undertaken to elucidate the intrinsic stability of an API. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

stress testing (of the finished pharmaceutical product (FPP)). Studies undertaken to assess the effect of severe conditions on the FPP. Such studies include photostability testing and specific testing on certain products (e.g. metered-dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

supporting stability data. Supplementary data, such as stability data on small-scale batches, related formulations, and products presented in containers not necessarily the same as those proposed for marketing, and scientific rationales that support the analytical procedures, the proposed retest period or the shelf life and storage conditions.

utilization period. See in-use period.

variations. A change to any aspect of a pharmaceutical product, including but not limited to, the change of use of a starting material, a change to formulation, method or site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.

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2. The following International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines (<http://www.ich.org>) may be consulted in the context of stability testing:
 - ICH Q1A (R2): Stability testing of new drug substances and products.
 - ICH Q1B: Photostability testing of new drug substances and products.
 - ICH Q1C: Stability testing of new dosage forms.
 - ICH Q1D: Bracketing and matrixing designs for stability testing of new drug substances and products.
 - ICH Q1E: Evaluation for stability data.
 - ICH Q2R1): Validation of analytical procedures: text and methodology.
 - ICH Q3A: Impurities in new drug substances.
 - ICH Q3B: Impurities in new drug products.
 - ICH Q5C: Quality of biotechnological products: stability testing of biotechnological/biological products.
 - ICH Q6A: Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances.
 - ICH Q7: Good manufacturing practice guide for active pharmaceutical ingredients.
 - ICH Q8: Pharmaceutical development.
 - ICH Q9: Quality risk management.
 - ICH Q11: Development and manufacture of drug substances (chemical entities and biotechnological/biological entities).
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10. Prequalification Programme – Priority Essential Medicines. A United Nations Programme managed by WHO. Information for applicants (<https://extranet.who.int/prequal/>).

Appendix 1

Examples of testing parameters

Section I for active pharmaceutical ingredients

In general, appearance, assay and degradation products should be evaluated for all active pharmaceutical ingredients (APIs). Since some related substances might only be identified as degradation products in the outcome of the stability studies, all specified related substances should be monitored as part of API stability studies. Other API parameters that may be susceptible to change should also be studied where applicable (e.g. particle size and/or polymorphism when relevant for low-solubility APIs).

Section II for finished pharmaceutical products

The following list of parameters for each dosage form is presented as a guide to the types of tests to be included in a stability study. In general, appearance, assay and degradation products should be evaluated for all dosage forms, as well as the preservative and antioxidant content if applicable.

The microbial quality of multiple-dose sterile and non-sterile dosage forms should be controlled. Challenge tests should be carried out at least at the beginning and at the end of the shelf life. Such tests would normally be performed as part of the development programme, for example, within primary stability studies. They need not be repeated for subsequent stability studies unless a change has been made which has a potential impact on microbiological status.

It is not expected that every test listed be performed at each time point. This can also apply to sterility testing, which may be conducted for most sterile products at least at the beginning and at the end of the stability test period. A validated container-closure integrity test may be used in lieu of sterility testing. Tests for pyrogens and bacterial endotoxins may be limited to the time of release. Sterile dosage forms containing dry materials (powder-filled or lyophilized products) and solutions packaged in sealed glass ampoules may need no additional microbiological testing beyond the initial time point. The level of microbiological contamination in liquids packed in glass containers with flexible seals or in plastic containers should be tested at least at the beginning and at the end of the stability test period; if the long-term data provided to the regulatory authorities for marketing authorization registration do not cover the full shelf-life period, the level of microbial contamination at the last time point should also be provided. Weight loss from plastic containers should be reported over the shelf life.

The list of tests presented for each dosage form is not intended to be exhaustive, nor is it expected that every test listed be included in the design of a stability protocol for a particular finished pharmaceutical product (FPP) (for example, a test for odour should be performed only when necessary and with due consideration for the analyst's safety).

The storage orientation of the product, i.e. upright versus inverted, may need to be included in a protocol when contact of the product with the closure system may be expected to affect the stability of the products contained (e.g. liquids or semisolids), or where there has been a change in the container-closure system.

Tablets

Dissolution, disintegration, water content and hardness/friability. Dispersible tablets should additionally be tested for disintegration (with a limit of not more than 3 minutes) and fineness of dispersion.

Capsules

- hard gelatin capsules: brittleness, dissolution, disintegration, water content and level of microbial contamination;
- soft gelatin capsules: dissolution, disintegration, level of microbial contamination, pH, leakage and pellicle formation.

Oral solutions, suspensions and emulsions

Formation of precipitate, clarity (for solutions), pH, viscosity, extractables, level of microbial contamination.

- Additionally for suspensions, dispersibility, rheological properties, mean size and distribution of particles should be considered. Also polymorphic conversion may be examined, if applicable.
- Additionally for emulsions, phase separation, mean size and distribution of dispersed globules should be evaluated.

Powders and granules for oral solution or suspension

Water content and reconstitution time.

Reconstituted products (solutions and suspensions) should be evaluated as described above under “Oral solutions suspensions and emulsions” after preparation according to the recommended labelling, through the maximum intended use period.

Metered-dose inhalers and nasal aerosols

Some parameters listed may be assessed during development and not be required subsequently in stability studies. Dose content uniformity, labelled number of medication actuations per container meeting dose content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate, level of microbial contamination, valve delivery (shot weight), extractables/leachables from plastic and elastomeric components, weight loss, pump delivery, foreign particulate

matter and extractables/leachables from plastic and elastomeric components of the container, closure and pump. Samples should be stored in upright and inverted/on-the-side orientations.

For suspension-type aerosols, microscopic examination of appearance of the valve components and the container's contents for large particles, changes in morphology of the API particles, extent of agglomerates, crystal growth, foreign particulate matter, corrosion of the inside of the container or deterioration of the gaskets.

Nasal sprays: solutions and suspensions

Clarity (for solution), level of microbial contamination, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet and/or particle size distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign particulate matter and extractables/leachables from plastic and elastomeric components of the container, closure and pump.

Topical, ophthalmic and otic preparations

Included in this broad category are ointments, creams, lotions, pastes, gels, solutions, eye drops and cutaneous sprays.

- Topical preparations should be evaluated for clarity, homogeneity, pH, suspendability (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible), level of microbial contamination/sterility and weight loss (when appropriate).
- Evaluation of ophthalmic or otic products (e.g. creams, ointments, solutions and suspensions) should include the following additional attributes: sterility, particulate matter and extractable volume.
- Evaluation of cutaneous sprays should include: pressure, weight loss, net weight dispensed, delivery rate, level of microbial contamination, spray pattern, water content and particle size distribution (for suspensions).

Suppositories

Disintegration and dissolution (at 37 °C) and as appropriate for the type, net filled content, rupture time, melting and solidification, liquefaction/softening time, leakage, pellicles and pH.

Small volume parenterals (SVPs)

Colour, clarity (for solutions), particulate matter, pH, sterility, endotoxins.

Stability studies for powders for injection solution should include monitoring for colour, reconstitution time and water content. Specific parameters to be examined at

appropriate intervals throughout the maximum intended use period of the reconstituted drug product, stored under condition(s) recommended on the label, should include clarity, colour, pH, sterility, pyrogen/endotoxin and particulate matter. It may be appropriate to consider monitoring of sterility after reconstitution into a product, e.g. dual-chamber syringe, where it is claimed that reconstitution can be performed without compromising sterility.

- The stability studies for suspension for injection should include, in addition, particle size distribution, dispersibility, specific gravity, resuspendability, rheological properties and dissolution (when applicable). Content uniformity may be considered a stability-indicating parameter for the primary stability studies of a depot injection such as depomedroxyprogesterone acetate (DMPA) (refer to the WHO Prequalification Team-medicines (PQTm) DMPA guidance document published on the PQTm website: who.int/prequal/).¹
- The stability studies for emulsion for injection should include, in addition, phase separation, viscosity, mean size and distribution of dispersed phase globules.

Large volume parenterals (LVPs)

Colour, clarity, particulate matter, pH, sterility, pyrogen/endotoxin and volume.

Transdermal patches

In vitro release rates, leakage, level of microbial contamination/sterility, peel and adhesive forces.

¹ https://extranet.who.int/prequal/sites/default/files/documents/46%20DMPA_Aug2015_0.pdf.

Appendix 2

Recommended labelling statements

1. Active pharmaceutical ingredients

The statements that should be used if supported by the stability studies for active pharmaceutical ingredients (APIs) are listed in Table A10.1.

Table A10.1

Recommended labelling statements for active pharmaceutical ingredients

Testing condition under which the stability of the API has been demonstrated	Recommended labelling statement ^a
25 °C/60% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 25 °C"
25 °C/60% RH (long-term) 30 °C/65% RH (intermediate, failure during accelerated stability studies)	"Do not store above 25 °C" ^b
30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
30 °C/75% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
5 °C ± 3 °C	"Store in a refrigerator (2 °C to 8 °C)"
-20 °C ± 5 °C	"Store in freezer"

^a During storage, shipment and distribution of the API, the current *Good trade and distribution practices (GTDP) for pharmaceutical starting materials* are to be observed (1). Details on storage and labelling requirements can be found in *WHO guide to good storage practices for pharmaceuticals* (2).

^b "Protect from moisture" should be added as applicable.

2. Finished pharmaceutical products

The statements that should be used if supported by the stability studies for finished pharmaceutical products (FPPs) are listed in Table A10.2.

Table A10.2**Recommended labelling statements for finished pharmaceutical products**

Testing condition under which the stability of the FPP has been demonstrated	Recommended labelling statement^a
25 °C/60% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 25 °C"
25 °C/60% RH (long-term) 30 °C/65% RH (intermediate, failure during accelerated stability studies)	"Do not store above 25 °C" ^b
30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
30 °C/75% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
5 °C ± 3 °C	"Store in a refrigerator (2 °C to 8 °C)"
-20 °C ± 5 °C	"Store in freezer"

^a During storage, shipment and distribution of the FPP, the current *good distribution practices (GDP) for pharmaceutical products* are to be observed (3). Details on storage and labelling requirements can be found in *WHO guide to good storage practices for pharmaceuticals* (2).

^b "Protect from moisture" should be added as applicable.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Additional labelling statements that could be used in cases where the result of the stability testing demonstrates limiting factors are listed in Table A10.3.

Table A10.3**Additional labelling statements for use where the result of the stability testing demonstrates limiting factors**

Limiting factors	Additional labelling statement, where relevant
Finished pharmaceutical products (FPPs) that cannot tolerate refrigeration	"Do not refrigerate or freeze" ^a
FPPs that cannot tolerate freezing	"Do not freeze" ^a
Light-sensitive FPPs	"Protect from light"

Table A10.3 *continued*

Limiting factors	Additional labelling statement, where relevant
FPPs that cannot tolerate excessive heat, e.g. suppositories	"Store and transport not above 30 °C"
Hygroscopic FPPs	"Store in dry condition"
Packaging (with the packaging format specified in the statement, e.g. bottle, blister)	<p>"Store in the original package"</p> <p>"Keep the container in the outer carton"</p> <p>"Keep the container tightly closed in order to protect from light and moisture"</p>

^a Depending on the pharmaceutical form and the properties of the FPP, there may be a risk of deterioration due to physical changes if subjected to low temperatures, e.g. liquids and semisolids. Low temperatures may also have an effect on the packaging in certain cases. An additional statement may be necessary to take account of this possibility.

References

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Appendix 3

Interpretation of storage statements for products approved in climatic zone II when the products are to be distributed in zone IV

In order to ensure the safe use of medicines in recipient countries, the wording on labelling storage statements must be considered in the context of both the region in and for which the stability studies were conducted and the region(s) in which the products are intended to be distributed.

For example, for products approved in a zone II region the stability testing has usually been conducted at accelerated conditions and at zone II long-term conditions. Demonstrated stability at zone II conditions may result in a label storage statement of "Store between 15 and 30 °C" in line with the convention of some zone II regions. A product with such a statement, received in a zone IV country, would be expected to have demonstrated stability at zone IVa or IVb long-term stability conditions. However, when the stability was demonstrated at zone II long-term conditions, the appropriate statement for distribution in a zone IV region would be "Do not store above 25 °C".

Typical examples of the storage statements for products approved in zone II, with examples of the stability data on which the statements are based and the corresponding WHO-recommended storage statement for distribution in zone IV are provided in Table A10.4.

Table A10.4

Examples of stability data and storage statements for products approved in climatic zone II and WHO-recommended storage statements (for zone IV) based on the same data

Storage statement for products approved in zone II	Examples of stability data on which the statements are based	WHO-recommended storage statement for products to be distributed in zone IVa
This medicinal product does not require any special storage conditions (or similar, i.e. no temperature mentioned) (EU)	Zone II + accelerated (finished pharmaceutical product (FPP) is stable at long-term conditions, with no significant change at accelerated conditions)	"Do not store above 25 °C. Protect from moisture"

Table A10.4 *continued*

Storage statement for products approved in zone II	Examples of stability data on which the statements are based	WHO-recommended storage statement for products to be distributed in zone IVa
This medicinal product does not require any special storage conditions (EU)	Zone II + Zone IVb + accelerated (FPP is stable at long-term conditions (zones II and IVb), with no significant change at accelerated conditions)	“Do not store above 30 °C”
Do not store above 30 °C (EU)	Zone IVa + accelerated (FPP is stable at long-term conditions, with significant change at accelerated conditions)	“Do not store above 30 °C, avoid excursions. Protect from moisture”
Store at 15 °C to 30 °C (USA, Canada) OR Store at 25 °C; excursions permitted to 15 °C to 30 °C (USA) OR Store at controlled room temperature (15–30 °C). (Canada)	Zone II + accelerated (FPP is stable at long-term conditions, with no significant change at accelerated conditions)	“Do not store above 25 °C. Protect from moisture”

Note: Zone II is 25 °C/60% RH, zone IVa is 30 °C/65% RH and zone IVb is 30 °C/75% RH.

Note: IVa may be acceptable in lieu of IVb when humidity is not an issue, for example, for storage in glass containers (see 2.2.7.2 of the main text of the Annex).

4.10 WHO guidelines for sampling of pharmaceutical products and related materials

**Annex 4, WHO Technical Report Series, 929,
2005**

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1. Introduction

These guidelines are primarily intended for use by governmental organizations, such as drug regulatory authorities (including inspectorates), quality control laboratories and customs and police officials, but some of the general principles may also be appropriate for application by procurement agencies, manufacturers and customers.

These guidelines should be useful when surveying the national markets for the quality of drug products in accordance with national drug quality surveillance programmes for marketed products, whether registered for sale or compounded in pharmacies.

The choice of a sampling plan should always take into consideration the specific objectives of the sampling and the risks and consequences associated with inherent decision errors. The bibliography at the end of this Annex should be consulted when justifying a sampling plan for a given purpose.

1.1 General considerations

Sampling comprises the operations designed to select a portion of a pharmaceutical product (for definition, see glossary) for a defined purpose. The sampling procedure should be appropriate to the purpose of sampling, to the type of controls intended to be applied to the samples and to the material to be sampled. The procedure should be described in writing.

All operations related to sampling should be performed with care, using proper equipment and tools. Any contamination of the sample by dust or other foreign material is liable to jeopardize the validity of the subsequent analyses.

1.2 Glossary

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

Available sample

Whatever total quantity of sample materials is available.

Batch

A quantity of any drug produced during a given cycle of manufacture. If the manufacturing process is continuous, the batch originates in a defined period of time during which the manufacturing conditions are stable and have not been modified.

Combined sample

Sample resulting from combining all or parts of two or more samples of the material.

Consignment

The quantity of a bulk starting material, or of a drug product, made by one manufacturer or supplied by an agent, and supplied at one time in response to a particular request or

order. A consignment may comprise one or more lot-identified packages or containers and may include material belonging to more than one lot-identified batch.

Final sample

Sample ready for the application of the test procedure.

Homogeneity

A material is regarded as homogeneous when it is all of the same origin (e.g. from the same batch) and as non-homogeneous when it is of differing origins.

Original sample

Sample collected directly from the material.

Pharmaceutical product

Any material¹ or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Prequalification

The activities undertaken in defining a product or service need, seeking expressions of interest from enterprises to supply the product or service, and examining the product or service offered against the specification, and the facility where the product or service is prepared against common standards of good manufacturing practice (GMP). The examination of the product or service and of the facility where it is manufactured is performed by trained and qualified inspectors against common standards. Once the product is approved, and the facility is approved for the delivery of the specified product or service, other procurement agencies are informed of the approval. Pre-qualification is required for all pharmaceutical products regardless of their composition and place of manufacture or registration, but the amount and type of information requested from the supplier for use in the assessment by the procurement agency may differ.

Production

All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

Random sample

Sample in which the different fractions of the material have an equal probability of being represented.

¹ "Material" is used in the document for "pharmaceutical products and related materials".

Representative sample

Sample obtained according to a sampling procedure designed to ensure that the different parts of a batch or the different properties of a non-uniform material are proportionately represented.

Retention sample

Sample collected as part of the original sampling process and reserved for future testing. The size of a retention sample should be sufficient to allow for at least two confirmatory analyses. In some cases statutory regulations may require one or more retention samples, each of which should be separately identified, packaged and sealed.

Sample

A portion of a material collected according to a defined sampling procedure. The size of any sample should be sufficient to allow all anticipated test procedures to be carried out, including all repetitions and retention samples. If the quantity of material available is not sufficient for the intended analyses and for the retention samples, the inspector should record that the sampled material is the available sample (see *Sampling record*) and the evaluation of the results should take account of the limitations that arise from the insufficient sample size.

Sampler

Person responsible for performing the sampling operations.

Sampling method

That part of the sampling procedure dealing with the method prescribed for withdrawing samples.

Sampling plan

Description of the location, number of units and/or quantity of material that should be collected, and associated acceptance criteria.

Sampling procedure

The complete sampling operations to be performed on a defined material for a specific purpose. A detailed written description of the sampling procedure is provided in the *sampling protocol*.

Sampling record

Written record of the sampling operations carried out on a particular material for a defined purpose. The sampling record should contain the batch number, date and place of sampling, reference to the sampling protocol used, a description of the containers and of the materials sampled, notes on possible abnormalities, together with any other relevant observations, and the name and signature of the inspector.

Sampling unit

Discrete part of a consignment such as an individual package, drum or container.

Selected sample

Sample obtained according to a sampling procedure designed to select a fraction of the material that is likely to have special properties. A selected sample that is likely to contain deteriorated, contaminated, adulterated or otherwise unacceptable material is known as an *extreme sample*.

Uniformity

A starting material may be considered uniform when samples drawn from different layers do not show significant differences in the quality control tests which would result in non-conformity with specifications. The following materials may be considered uniform unless there are signs to the contrary: organic and inorganic chemicals; purified natural products; various processed natural products such as fatty oils and essential oils; and plant extracts. The assumption of uniformity is strengthened by homogeneity, i.e. when the consignment is derived from a single batch.

1.3 Purpose of sampling

Sampling may be required for different purposes, such as pre- qualification; acceptance of consignments; batch release testing; in-process control; special controls; inspection for customs clearance, deterioration or adulteration; or for obtaining a retention sample.

The tests to be applied to the sample may include:

- verifying the identity;
- performing complete pharmacopoeial or analogous testing; and
- performing special or specific tests.

1.4 Classes and types of pharmaceutical products and related materials

The materials to be sampled may belong to the following classes:

- starting materials for use in the manufacture of finished pharmaceutical products;
- intermediates in the manufacturing process (e.g. bulk granule);
- pharmaceutical products (in-process as well as before and after packaging);
- primary and secondary packaging materials; and
- cleaning and sanitizing agents, compressed gases and other processing agents.

1.5 Sampling facilities

Sampling facilities should be designed to:

- prevent contamination of the opened container, the materials and the operator;
- prevent cross-contamination by other materials, products and the environment; and
- protect the individual who samples (sampler) during the sampling procedure.

Where possible, sampling should be performed in an area or booth designed for and dedicated to this purpose, although this will not be possible where samples are required to be taken from a production line (e.g. in-process control samples). The area in which the sample was taken should be recorded in the sampling record and a sequential log should be kept of all materials sampled in each area.

Sampling from large containers of starting material or bulk products can present difficulties. Whenever possible, this work should be carried out in a separate, closed cubicle within the warehouse, to reduce the risk of contamination (e.g. by dust) of either the sample or the materials remaining in the container, or of cross-contamination.

Some materials should be sampled in special or dedicated environments (e.g. when sampling articles for which contamination with dirt or particles from the environment should be avoided, such as aerosol valves, hormones and penicillins).

Generally, taking the original sales pack as a sample from outlets such as pharmacies or hospitals does not present problems. However, the inspector should ensure that the quantity of sample taken is sufficient for the intended analyses and for the retention samples, and that all units sampled are derived from the same batch and preferably from the same location.

1.6 Responsibilities for sampling

Those responsible for sampling procedures include:

- *governmental organizations*, such as drug control authorities (including inspectorates); quality control laboratories; customs and police authorities responsible for the clearance of drug products held in quarantine after manufacture or importation, and for the detection of pharmaceutical products that have deteriorated or have been contaminated, adulterated or counterfeited;
- *customers* such as governmental or nongovernmental agencies involved in the acquisition of drug products; and
- *manufacturers* in the context of good manufacturing practices (GMP).

The samplers need to be adequately trained in the practical aspects of sampling, qualified to perform the sampling operation, and should have sufficient knowledge of pharmaceutical substances to allow them to execute the work effectively and safely. Given that the sampling technique itself can introduce bias, it is important that personnel carrying out the sampling should be suitably trained in the techniques and procedures used. The training should be documented in the individual's training records. Sampling records should clearly indicate the date of sampling, the sampled container and the identity of the person who sampled the batch.

A conscientious approach, with meticulous attention to detail and cleanliness, is essential. The sampler should remain alert to any signs of contamination, deterioration or tampering. Any suspicious signs should be recorded in detail in the sampling record.

If a governmental agency needs to sample a sterile or bulk pharmaceutical product at the manufacturing site, it may be best to have the manufacturer's personnel collect the sample, using their own procedures. The regulatory inspector would observe the procedure in such a way as not to increase the chance of contamination (e.g. for sterile pharmaceutical products, the inspector would observe through a glass window outside the aseptic sampling area) and to preclude the possibility of the inspector inadvertently contaminating the remaining bulk pharmaceutical product through poor procedures, for example.

1.7 Health and safety

It is the responsibility of the sampler to read the relevant health and safety information (e.g. the safety data sheet for a pharmaceutical product and related materials) before sampling the material. The information should include necessary safety precautions and requirements for both the operator and the environment.

The sampler should wear appropriate protective clothing for the task. If specific safety precautions are required, such as the use of respiratory equipment, the sampler should be properly trained in its use.

The sampler should have safe access to and egress from the place where the sample is taken, and the places where the samples are taken for storage. The sample storage areas should have adequate light and ventilation and should be arranged to satisfy the requirements for safety as well as any special ones arising from the characteristics of the material being sampled.

Care should be taken to guard against collapse of stacked containers or solids in bulk.

2. Sampling process

2.1 Preparation for sampling

For the sampling of products, the responsible person should have at his or her disposal all the tools needed to open the containers (e.g. packages, barrels and others). Tools may include knives, pliers, saws, hammers, wrenches, implements to remove dust (preferably a vacuum cleaner), and material to reclose the packages (such as sealing tape), as well as self-adhesive labels to indicate that some of the contents have been removed from a package or container. Containers due to be sampled should be cleaned prior to sampling if necessary.

Sampling of uniform starting materials does not require complicated tools. A variety of pipettes fitted with suction bulbs, cups or beakers, dippers and funnels are needed for liquids of low viscosity. The use of glass should be avoided. A suitable inert rod can be used for highly viscous liquid, and spatulas or scoops are needed for powdered and granular solids. Sterile pharmaceutical products should be sampled under aseptic conditions, and only when deemed absolutely essential, to avoid the risk of loss of sterility.

The tools for sampling non-uniform materials are more complicated and more difficult to clean. For example, a sampling tube with a shutter at the lower end may be used to sample liquids in drums or other large containers and a slotted tube with a pointed end may be used to sample solids. It is important to follow the manufacturer's instructions for the use of sampling devices.

All sampling tools and implements should be made of inert materials and kept scrupulously clean. After use or before reuse, they should be thoroughly washed, rinsed with water or suitable solvent, and dried. They should be stored in clean conditions. Adequate washing facilities should be provided in, or in close proximity to, the sampling area, otherwise samplers will need to bring separate clean sets of implements for sampling each product. The cleaning procedure used for all sampling tools and implements should be documented and recorded. The adequacy of the cleaning procedure for the material from which the sampling tool is made should be demonstrated. The use of disposable sampling materials has distinct advantages.

Examples of sampling tools suitable for each type of material are given in Appendix 1.

2.2 Sampling operation and precautions

There should be a written procedure describing the sampling operation. This should include details of the health and safety aspects of sampling. It should ensure that representative samples are taken in sufficient quantity for testing in accordance with specifications. Closures and labels should preferably be such that unauthorized opening can be detected. Samples should never be returned to the bulk.

The sampling process should be appropriately supervised and documented (see Appendix 2 for an example of a sample collection form).

The sampling procedure should be such that non-uniformity of the material can be detected. During the sampling procedure, attention should be paid to any signs of nonconformity of the material.

Signs of non-uniformity include differences in shape, size or colour of particles in crystalline, granular or powdered solid substances; moist crusts on hygroscopic substances; deposits of solid pharmaceutical product in liquid or semi-liquid products; and stratification of liquid products. Such changes, some of which may be readily reversible, can occur during prolonged storage or exposure to extreme temperatures during transportation. Homogeneous portions of the material or bulk such as those mentioned above should be sampled and tested separately from the rest of the material that has a normal appearance.

Pooling of the samples from the different portions should be avoided, because this can mask contamination, low potency or other quality problems.

Labelling of samples should provide appropriate details, including the batch number and, if known, the container number from which the sample was taken, the amount taken and for what purpose. Labels should be applied at the time of sampling. The container used to store the sample should also be properly labelled with appropriate details such as sample type, name of material, identification code, batch/lot number, code, quantity, date of sampling, storage conditions, handling precautions and container number.

For finished drug products, the sampling procedure should take account of the official and non-official tests required for the individual dosage form (e.g. tablets or parenteral preparations). Non-official tests could include testing for adulteration and counterfeiting.

The sampling procedure should also take account of past experience with the pharmaceutical product or related material and with the supplier, and of the number of sampling units in the consignment.

Examples of steps for sampling are given in Appendix 3.

When a container is sampled outside the control of the consignee of the product, the following precautions should be taken. If the tamper-proof seal is broken to obtain a sample, then the consignee of the product should be informed and the container resealed with an appropriate tamper-proof seal, and the consignee of the product informed of its type and its identification. If a bag has been punctured to take a sample, then the sampling hole should be appropriately closed and identified as a sampling hole made by an authorized sampler. Sampled containers should be identified, as they may no longer contain the quantity of product stated on the label. In accordance with national legislation there may be exceptions, e.g. during ongoing investigations of cases related to counterfeit pharmaceutical products.

2.3 Storage and retention

The container used to store a sample should not interact with the sampled material nor allow contamination. It should also protect the sample from light, air and moisture, as required by the storage directions for the pharmaceutical product or related material sampled. As a general rule the container should be sealed and preferably tamper-evident.

Samples of loose materials, whether solid or liquid, should be placed in one or more clean containers. Liquid samples should be transported in suitable bottles closed by screw tops with inert liners that provide a good vapour-proof (moisture-proof) seal for the contents. Suitable screw-top jars in exceptional cases only should be used for solid or semi-solid pharmaceutical products. The container should be inert. Light-sensitive materials should be protected by using amber glass containers or by wrapping colourless glass containers in foil or dark-coloured paper. Headspace should be kept to a minimum to minimize any possible degradation. Any special procedures, for example, nitrogen gassing, should be discussed with the consignee of the material and carried out as appropriate.

Solid dosage forms such as tablets or granules should be protected during transit, either by totally filling the container with the product or by filling any residual space with a suitable material. All containers should be sealed and labelled, and all samples should be packaged adequately and transported in such a way as to avoid breakage and contamination during transport.

For all containers that come apart (e.g. screw-capped jars or metal tins with separate lids) precautions should be taken to avoid any mix-up when they are opened for examination, such as by labelling all parts of each container whenever possible.

If one sample is divided into several sample containers, they should be transported in a suitably sealed box, which should be labelled with the identity of the product, the consignment from which the sample was drawn, the size of the sample, the date and place of sampling, and the name of the inspector.

Security and adequate storage conditions should be ensured for the rooms in which samples are stored. Samples should be stored in accordance with the storage conditions as specified for the respective active pharmaceutical ingredient (API), excipient or drug product. Packaging materials similar to those in which the bulk is supplied should be used for long-term storage.

Examples of types of containers used to store samples of starting materials and bulk products are given in Appendix 4.

3. Regulatory issues

When sampling for regulatory purposes, additional samples for regulatory testing and verification purposes should be provided (e.g. for duplicate testing and parallel testing by different regulatory laboratories and by the consignee of the product). The

consignee of the product should be informed that samples have been taken, and should the consignee wish to conduct his/her own testing of the sample taken for regulatory purposes, regulatory authorities should provide a sample to the consignee of the goods.

Sampling of products for prequalification purposes may follow similar procedures.

3.1 Pharmaceutical inspections

Pharmaceutical inspectors may take samples from retail or hospital pharmacies (including samples of preparations manufactured in bulk on the premises), or from industry and wholesalers for a variety of reasons, such as:

- routine monitoring and control;
- following the suspicion or discovery of products that show signs of possible deterioration, contamination, adulteration or counterfeiting; and
- when a particular product is suspected of being either ineffective or responsible for adverse clinical reactions.

For deteriorated dosage forms, the sample should consist of one or more retail containers of the product that shows visual signs of deterioration.

When a complaint has been received about a drug product, the sample should include the original container and, if possible, one or more unopened containers containing the same product and bearing the same batch number. There should be good communication between the regulatory authority and the consignee of the goods concerning the findings and any necessary corrective action.

3.2 Surveillance programmes

National drug regulatory authorities are responsible for monitoring the quality of all drug products marketed in their country and as defined by legislation. The extent to which routine surveillance should be undertaken, as opposed to assessment of suspect products, will depend upon factors such as:

- the capacity of the national quality control laboratory;
- the extent to which the quality of the product has been assessed prior to registration;
- the extent to which the requirements for GMP are implemented; and
- the number of products that are imported from abroad.

A systematic programme of drug quality surveillance should be in place which may include sampling of marketed products, whether registered for sale or compounded in pharmacies, as deemed necessary. Each product should be assessed regularly (e.g.

every 2–3 years) for inclusion in the surveillance programme, but particular attention should be accorded to products that are of prime importance to public health programmes or that are potentially dangerous, unstable or difficult to formulate properly.

The responsible laboratory should draw up the sampling programme, if necessary under the guidance of the drug regulatory authority, on a yearly or half-yearly basis. This programme should not only list the products to be sampled during a given period, but should also specify the sampling procedures and the size of the samples to be collected, taking into account the need for retention samples. The programme should state to what extent each brand of a given product will be sampled and which local authority or inspector will be responsible for each sampling operation. It should indicate to which laboratory (if more than one exists) each sample should be sent. Such a programme enables the facilities of each laboratory to be used to best advantage.

4. Sampling on receipt (for acceptance)

4.1 Starting materials

Testing of starting materials should be undertaken using samples collected in accordance with an appropriate procedure.

If the material of a consignment can be regarded as uniform, the sample can be taken from any part of the consignment. If, however, the material is not physically uniform, special sampling tools may be required to withdraw a cross-sectional portion of the material. Alternatively, where applicable, a validated procedure can be followed to restore the uniformity of the material before sampling, based on information concerning the subsequent handling and manufacturing steps. For example, a stratified liquid may be stirred or a solid deposit in a liquid may be dissolved by gentle warming and stirring. Such interventions should not be attempted without adequate knowledge of the properties of the contents and appropriate discussions with the consignee of the goods.

All partially processed natural products, both animal, herbal (dried plants and their parts) and mineral, should be treated as intrinsically non-uniform. Special procedures requiring considerable practice are needed to prepare representative samples from such consignments, including coning and quartering and the treatment of fines. Details of appropriate procedures may be found in the relevant International Organization for Standardization (ISO) documents (see Bibliography). These procedures are not further described in these guidelines.

4.2 Intermediates in the manufacturing process and bulk pharmaceutical products

Pharmaceutical intermediates and products supplied in bulk may need to be examined. These include liquids and semi-solid pharmaceutical products, powdered solids or granulates transported in large containers and intended either for further processing

or for direct packaging into final market containers, and unit dosage forms (tablets, capsules) supplied in bulk which are intended for repackaging into smaller containers.

There is a risk of segregation of bulk materials during transportation and this should be taken into account when drawing up the sampling plan.

Products of this kind may be assumed to be uniform where the transportation process has been validated, provided that they:

- are labelled with the name of the manufacturer and a single batch number;
- have been produced in accordance with GMP; and
- are supplied with a certificate, issued in the country of origin, according to the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce.

In these circumstances the collection of a single sample, sufficient for the intended analyses, is adequate.

4.3 Finished products

The quality of finished pharmaceutical products frequently needs to be verified at the time of their importation or purchase. The necessary sampling should be performed using an appropriate method and with regard to the presumed uniformity. A single consignment of a product from a single manufacturer and labelled with a single batch number may be assumed to be uniform.

The minimum size of the samples will be determined by the requirements of the analytical procedure that will be used to test the product. Tests of unit dosage forms for uniformity of weight, volume or content can require a considerable number of units, as can tests for sterility. Depending upon the type of material, the size of the consignment and the way in which the material is packed, a unit to be sampled may be regarded as the transport container, e.g. 20 packs shrink-wrapped or boxed together, rather than an individual container. The required number of unit dosage forms is then withdrawn from any individual container in the selected transit container.

Sampling and testing may be adjusted according to experience with the specific source (e.g. manufacturer or supplier) of the product. If the consignment consists of one very large batch, or if little experience has been obtained with the product to be sampled, it may be prudent to carry out two independent analyses. Two independent final samples should then be taken from different sampling units. Conversely, when a consignment is composed of two or three batches from the same manufacturer, a single sample taken from each batch may suffice, provided that favourable documented experience has previously been gained with the product and the manufacturer, and that there is evidence from the expiry date, or other information, that the batches were produced at approximately the same time.

Note: When sampling finished products, packaging materials may be retained for testing.

4.4 Packaging materials (primary and secondary)

There is a potential for mixing up printed packaging materials during the sampling operations and, therefore, only one material should be handled at a time. Also, samples of packaging materials should never be returned to the consignment.

Adequate protection (e.g. collapsible metal tubes) and identification should be provided for the sample to avoid mixing or damage.

Primary packaging materials should be adequately protected during the sampling operation to avoid environmental contamination. The final use of the packaging should be taken into consideration and appropriate sampling protection afforded (e.g. in the sampling of parenteral ampoules). There are several reasons why a consignment of packaging materials may not necessarily be considered homogenous; for example:

- Materials were manufactured on different days or machines.
- Materials were manufactured on one machine, but on different stations (e.g. 16 printing dye stations or 12 moulding stations).
- Packaging was manufactured with different source materials (e.g. polyethylene from two different sources).
- A change of quality occurred during the process (e.g. container-wall thickness, colour variation, text legibility or change of printing plate).

It is, therefore, important at least to take random samples (e.g. from across the consignment), and to consider focused sampling, taking into account some of the above points.

5. Sampling plans for starting materials, packaging materials and finished products

As stated in the introduction, these guidelines are intended primarily for drug regulatory authorities and procurement agencies. The following sampling plans are, therefore, not necessarily appropriate for manufacturers, although the guiding principles may be useful. The choice of the sampling plan should always take into consideration the specific objectives of the sampling and the risks and consequences associated with inherent decision errors. It should be noted that sampling plans are not recommended for sampling of starting materials for identification tests (see *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Volume 2, Updated edition. Good manufacturing practices and inspection*. Geneva, World Health Organization, 2004; and *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth report*. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929, Annex 2)).

Ideally each sampling unit should be examined to ensure that it is intact and also checked for possible damage to the container. The contents should be inspected for uniformity and appropriately tested for identity. Uniformity should be tested on selected layer samples at different points in the material without previous intermixing. However, in cases when this ideal procedure is not possible or justified by the purpose of sampling, a number of sampling units should be randomly selected for sampling. It is not prudent to open all containers of products, which are liable to deteriorate under the influence of moisture or oxygen when held in a transit warehouse. However, materials in damaged containers or those found to be non-uniform should either be rejected or individually sampled for a complete quality control. Unlabelled sampling units should be rejected.

Table 1
Values of n , p or r for the N sampling units^a

Value of n , p or r	Values of N		
	n plan	p plan	r plan
2	up to 3	up to 25	up to 2
3	4–6	26–56	3–4
4	7–13	57–100	5–7
5	14–20	101–156	8–11
6	21–30	157–225	12–16
7	31–42		17–22
8	43–56		23–28
9	57–72		29–36
10	73–90		37–44

^a An example of how these plans work is given in Appendix 5.

For random sampling, whenever possible each sampling unit should be consecutively numbered and the required number of random sampling units selected using tables of random numbers.

The number of units to be sampled depends on different assumptions and three possible plans are shown in Table 1. For more comprehensive, statistically-based sampling schemes, see Bibliography.

It is important to recognize that the “ n -plan” is not statistically based and should be used only as a guiding principle.

5.1 Starting materials

When sampling starting materials proper consideration has to be given to deciding on a sampling plan. The following are examples of sampling plans that could be used.

5.1.1 *The n plan*

The “*n* plan” should be used with great caution and only when the material to be sampled is considered uniform and is supplied from a recognized source. Samples can be withdrawn from any part of the container (usually from the top layer). The *n* plan is based on the formula $n = 1 + \sqrt{N}$, where N is the number of sampling units in the consignment. The value of *n* is obtained by simple rounding. A minimum number of containers needs to be sampled, e.g. if N is less than or equal to 4, then every container is sampled. According to this plan, original samples are taken from *n* sampling units selected at random and these are subsequently placed in separate sample containers. The control laboratory inspects the appearance of the material and tests the identity of each original sample according to the relevant specification. If the results are concordant, the original samples are combined into a final, composite sample from which an analytical sample is prepared, the remainder being kept as a retention sample.

Note: The *n* plan is not recommended for use by control laboratories of manufacturers who are required to analyse and release or reject each received consignment of the starting materials used to produce a drug product.

5.1.2 *The p plan*

The “*p* plan” may be used when the material is uniform, is received from a recognized source and the main purpose is to test for identity. The *p* plan is based on the formula $p = 0.4 \sqrt{N}$, where N is the number of sampling units. The figures for *p* are obtained by rounding up to the next highest integer. According to this plan, samples are taken from each of the N sampling units of the consignment and placed in separate sample containers. These original samples are transferred to the control laboratory, visually inspected and tested for identity (a simplified method may be used). If the results are concordant, *p* final samples are formed by appropriate pooling of the original samples.

5.1.3 *The r plan*

The “*r* plan” may be used when the material is suspected to be non-uniform and/or is received from a source that is not well known. The *r* plan may also be used for herbal medicinal products used as starting materials. This plan is based on the formula $r = 1.5\sqrt{N}$, where N is the number of sampling units. The figures for *r* are obtained by rounding up to the next highest integer.

Samples are taken from each of the N sampling units of the consignment and placed in separate sample containers. These original samples are transferred to the control laboratory and tested for identity. If the results are concordant, r samples are randomly selected and individually subjected to testing. If these results are concordant, the r samples are combined for the retention sample.

5.2 Packaging materials

Sampling plans for packaging materials should be based on defined sampling standards, for example, British Standard BS 6001-1, ISO 2859 or ANSI/ASQCZ1.4-1993.

The objective is to ensure that there is a low probability of accepting material that does not comply with the predefined acceptance level.

5.3 Finished products

As for packaging materials, sampling plans for finished products should be based on defined sampling standards such as BS 6001-1, ISO 2859 or ANSI/ASQCZ 1.4-1993.

In some cases it may be sufficient to limit examination of finished goods to visual inspection only. If physical and chemical testing is required, however, the sampling units should consist of whole packs. Individual packs should not be broken open for the purposes of sampling.

An example of the steps to be considered when sampling finished products is given in Appendix 3, based on the sampling plans given in ISO 2859-1.

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Appendix 1

Types of sampling tools

Scoops

Small containers of solid materials may be adequately sampled using a spatula or scoop. The samples are then blended to provide a representative sample of that container. Figure 1 shows the recommended designs of scoops, which should preferably be rounded.

Figure 1
Sampling scoops for solids



If the scoop used is too small for the sizes of particle being sampled, large particles will roll off and testing bias may be introduced. On the other hand, if the scoop is too big, an unnecessarily large sample will be obtained for a given number of increments.

A scoopful of sample should be taken in a single movement and transferred to the sample container. Avoid tapping the scoop to remove pharmaceutical product as this is likely to cause segregation of the sample.

Dip tubes

Dip tubes should be used for sampling liquid and topical products and should be made of an inert material, such as polypropylene or stainless steel. A typical dip tube is shown in Figure 2.

Figure 2
Typical dip tube



Weighted containers

For taking samples from large tanks and storage vessels, a container in a weighted carrier can be used. The container is designed such that it can be opened at the required depth. Marks on the cord used for lowering the container can be used to determine when the correct sampling depth has been reached. A typical weighted container is shown in Figure 3.

Thieves

Sample thieves should be used when taking samples from deep containers of solids. Typical thieves are shown in Figure 4.

The plug thief typically consists of a hollow tube with an inner rod that has a tip on the end to allow the thief to enter the powder bed in the closed position (see Figure 4.i). The geometry of this tip can influence the sample taken; pointed tips distort the powder bed less than blunt-tipped probes, thereby reducing sampling error. Some thieves have a locking device that allows the sample volume to be set to the required sample weight, thereby reducing the weight variation in the sample population.

Figure 3
Typical weighted container

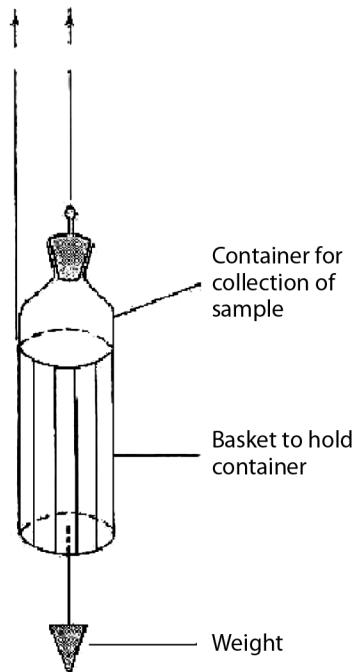
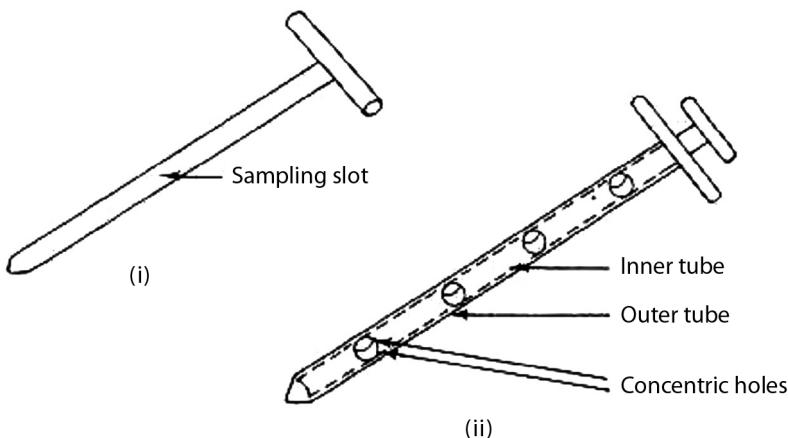


Figure 4
Typical sample thieves



A chamber thief generally consists of two concentric tubes (see Figure 4.ii); the inner tube is solid except for the chambers in which the sample is collected. The outer tube is hollow with openings that can be aligned with the chambers in the inner tube. A well-designed thief will have a sharp end to minimize disruption to the powder bed. When it is inserted into a static powder blend a thief will distort the bed by carrying pharmaceutical product from the upper layers of the blend to the lower layers. The magnitude of this distortion can depend on whether the thief is inserted into the blend with a smooth, jerky or twisting action. Therefore, the correct sampling procedure should be defined and staff trained in using the appropriate technique. Thieves are also sometimes referred to as "double-tube spears".

The angle at which the thief enters the powder bed can also influence sampling error. If a thief is inserted into the powder bed vertically, it can extract samples of different particle size from those that would be obtained using the same thief inserted at an acute angle. In addition the orientation of a chamber thief in relation to the powder bed (i.e. whether the chamber is at the top, the bottom or in the middle of the thief) may also influence the sampling error.

The material from which the thief is constructed, e.g. stainless steel or polypropylene, may also have an effect on sampling error due to static effects.

Sampling error can also be affected by bed depth, as the static pressure of the bulk blend forces the material into the sample chamber(s). This pressure is far greater at the bottom of a large container than it is in the middle or at the top. It is quite possible that the same thief could extract samples of different particle size from the top or bottom of a static powder blend.

Simple bag-sampling spears

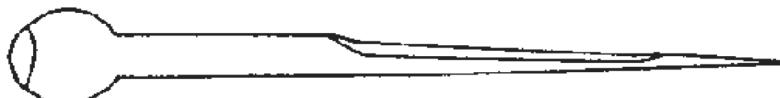
Simple bag-sampling spears are the most commonly used instruments for taking samples from bags, because they are relatively cheap, simple and quick. Sampling spears generally have a maximum external diameter of about 12 mm, but can be up to 25 mm in diameter. To obtain a good cross-sectional sample, the spear should be 40–45 cm in length. The tapered type of sampling spear penetrates bags easily. Typical spears are shown in Figure 5.

Figure 5
Typical sampling spears

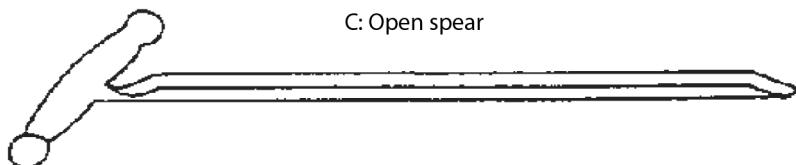
A: Closed spear for sampling large grains such as maize



B: Closed spear for sampling small grains such as wheat



C: Open spear



D: Double-tube spear



Appendix 2

Sample collection form^a

Serial number: _____

Name of location/place where sample was taken:

Address (with telephone and fax number, if applicable):

Date of sampling: _____

Names of people who took samples:

1. _____
2. _____

Product name of the sample: _____

Name of (active) starting material (INN, generic or scientific name) with dosage strength: _____

Dosage form (tablet, capsule, etc.): _____

Batch/lot number: _____

Date of manufacture: _____ Expiry date: _____

Registration or licence number (if applicable): _____

Name of the manufacturer: _____

Number of sample unit taken (tablet, capsule, etc.: at least 20 but not more than 30 units): _____

^a This sample collection form should always be kept with the sample collected. Proper sampling procedures should be followed.

Brief physical/visual description of sample:

Signature of person(s) taking samples

1. _____

2. _____

Signature of representative of the
establishment where sample(s) was
taken (optional)

Appendix 3

Steps to be considered for inclusion in a standard operating procedure

The steps for inclusion in a standard operating procedure described below are derived on a purely theoretical basis and are presented for information purposes only.

Bulk liquid products

The steps to be considered when sampling bulk liquid products are as follows.

1. Read and understand the precautions to be observed for the safe handling of the material.
2. Gather together the required sampling equipment (sampling tube or weighted sampling can, sample bottles and labels) and check that all the required items are clean.
3. Locate the batch.
4. Examine the container(s) for signs of contamination of the batch. Record any faults.
5. Examine the labels for obvious differences and signs of changes including obliterations and mislabelling. Record any faults.
6. Investigate and clarify the sources of and reasons for any faults before proceeding.
7. Choose a liquid-sampling tube of size and orifice suitable for the viscosity of the liquid being sampled.
8. Sample the liquid, suspension or emulsion (well stirred, if appropriate) by slowly pushing the open sampling tube vertically down-wards through the liquid so that material is collected from each layer.
9. Seal the tube, withdraw it from the bulk liquid, and allow liquid adhering to the outside of the tube to drain. Transfer all the contents of the tube to a clean, labelled sample bottle.
10. Repeat steps 8 and 9 until sufficient samples for analytical and retention purposes have been obtained.
11. Seal the sample bottle.
12. Reseal the container from which the samples were taken and label as “sampled”.
13. Clean and dry the sampling tube, observing the relevant safety precautions.

14. Sample other required containers in the same manner following steps 8–12 above.
15. Clean the sampling tube using the recommended cleaning procedure.
16. Deliver the analytical samples to the laboratory and the reserve samples to the retention sample store. Report any aspects of the sampling that should be brought to the attention of the analyst or the inspector.
17. Check supplier certificate versus the specifications, if applicable.

Powdered starting material

The steps to be considered in sampling a powdered starting material are as follows.

1. Read and understand the precautions to be observed for the safe handling of the material.
2. Gather together the required sampling equipment (sampling spear, sample bottles and labels) and check that all items are clean.
3. Locate the consignment and count the number of containers. Record this number.
4. Examine all the containers for obvious differences and signs of damage. Record any faults.
5. Examine all the labels for obvious differences and signs of changes, including obliterations and mislabelling. Record any faults.
6. Segregate any damaged containers and those with suspected spoiled contents for separate examination. These should then be *referred* or *rejected* and dealt with accordingly.
7. Segregate any containers with different batch numbers and treat these separately.
8. Number the remaining containers.
9. Choose the appropriate sampling plan (n , p or r).
10. Choose the containers to be sampled in accordance with the requirements of the chosen plan (by the use of random number tables, by drawing lots or by the use of a random number generator if applicable).
11. Open the containers one at a time and inspect the contents. Record any differences.
12. Choose a suitable, clean sampling spear and plunge this (gates closed) into the powder so that the point of the spear reaches the bottom of the container.
13. Open the gates to allow the powder to enter the spear cavities, then reclose them.

14. Withdraw the spear from the container and transfer the spear contents to a labelled sample bottle.
15. Repeat steps 12–14 until sufficient material has been collected for analytical and retention requirements.
16. Seal the sample bottle.
17. Reseal the container from which the samples were withdrawn and label as “sampled”.
18. Wipe clean the sampling spear if required, observing the safety precautions, before sampling the other chosen containers.
19. Repeat steps 12–18 for each chosen container.
20. Clean the sampling spear using the recommended cleaning procedure.
21. Deliver the analytical samples to the laboratory and the reserve samples to the retention sample store. Report any aspects of the sampling that should be brought to the attention of the analyst or inspector.
22. Check the supplier certificate versus the specifications, if applicable.

Packaging materials

The steps to be considered in sampling packaging materials are as follows.

1. Check the consignment against any associated documentation.
2. Check transit containers for the following and report any deviations as necessary:
 - 2.1 correct identification;
 - 2.2 integrity of seal, if appropriate; and
 - 2.3 absence of physical damage.
3. Obtain the required sample from the required number of containers, bearing in mind the special considerations for sampling packaging materials noted in section 4.4 of this Annex.
4. Place the sample units into identified appropriate sample containers.
5. Identify the consignment containers that have been sampled.
6. Note any special situations found during the sampling process (e.g. rogue items or component damage). Report any such observations as necessary.
7. Remove all sampled material pallets or containers from the sampling area together with all documentation.
8. Check supplier certificate against the specifications, if applicable.

Finished products

The following steps should be considered when sampling finished products.

1. Determine the number of pallets per batch in the consignment.
2. Work out as per ISO 2859–1 table level II, the number of pallets to be checked visually.
 - 2.1 Check condition of pallet and packaging for integrity of outer packaging material.
 - 2.2 Check outside of goods on the pallets for general cleanliness.
 - 2.3 Check that the overall labelling of the pallets matches the packing list.
 - 2.4 Count, categorize and record the number of defects.
3. Count the total number of transport packs on the number of pallets present and verify the total against the packing list.
4. From the number of pallets work out the number of transport packs to be sampled using the ISO table.
 - 4.1 Check condition of boxes for integrity of packaging material.
 - 4.2 Check for cleanliness of boxes.
 - 4.3 Check the labelling of the boxes for damage.
 - 4.4 Check the boxes for overall damage.
 - 4.5 Check the labels for spelling mistakes.
 - 4.6 Check the labels for manufacturing and expiry dates.
 - 4.7 Count, categorize and record the number of defects.
5. From the number of boxes selected work out the number of unit packs to be examined visually using the ISO table.
 - 5.1 Check condition of the containers for integrity of packaging material.
 - 5.2 Check for cleanliness of containers.
 - 5.3 Check condition of containers for shape and colour.
 - 5.4 Check the labelling of containers for damage.
 - 5.5 Check the containers for overall damage.
 - 5.6 Check the labels for spelling mistakes.
 - 5.7 Check the labels for manufacturing and expiry dates.
 - 5.8 Count, categorize and record the number of defects.
6. From the number of containers selected, determine the number of containers to be taken for physical and chemical testing and for retention.
7. Check the supplier certificate against the specifications, if applicable.

Appendix 4

Examples of types of containers used to store samples of starting materials and bulk products

Figure 1
Bag for storage of samples

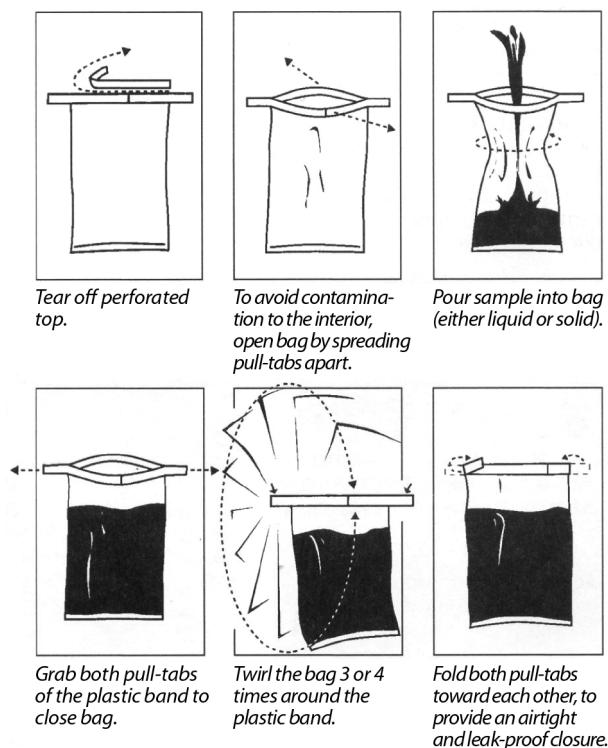
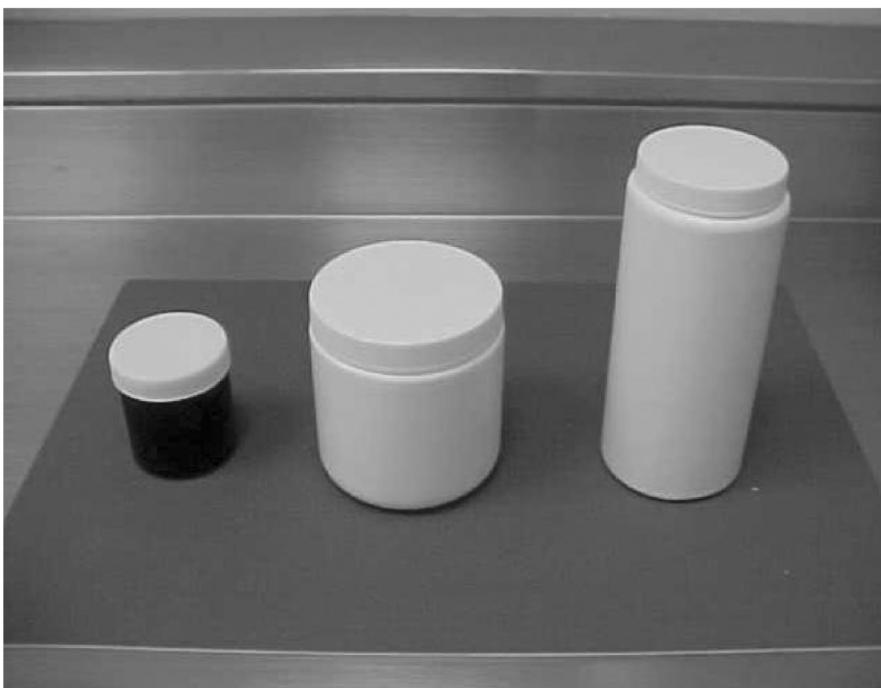


Figure 2
Screw-top containers



Appendix 5

Examples of use of sampling plans n , p and r

Consider a consignment of 40 containers of a starting material.

n Plan

Assuming a uniform material from a recognized source where there is a high degree of confidence in the source

Using the n plan, samples would be taken from seven containers selected at random. The appearance and identity of each of these seven samples is checked. If the results are concordant, the seven samples are combined to produce a single, composite sample from which an analytical sample is prepared for full testing.

p Plan

Assuming a uniform material from a recognized source with the main purpose of checking the identity

Using the p plan, samples would be taken from each container. The appearance and identity of each of these samples is checked. If the results are concordant, the samples are appropriately combined to form three final, composite samples to be used for retention (or full testing if required).

r Plan

Assuming the material is non-uniform and/or from a source that is not well-known

Using the r plan, samples would be taken from each container. The appearance and identity of each of these samples is checked. If the results are concordant, 10 samples are selected at random and individually subjected to full testing.

4.11 Guidelines on packaging for pharmaceutical products

Annex 9, WHO Technical Report Series, 902,
2002

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Introductory note

This review of the various elements of the packaging of a pharmaceutical product is aimed at ensuring that medicines arrive safely in the hands of the patients for whom they are prescribed.

In the manufacture of pharmaceutical products, quality assurance is defined as “the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use” (1).

In addition, the system of quality assurance for the manufacture of pharmaceutical products should ensure that “arrangements are made for the manufacture, supply and use of the correct starting and packaging materials” (1).

Public opinion sometimes considers packaging to be superfluous. However, it must be emphasized that packaging preserves the stability and quality of medicinal products and protects them against all forms of spoilage and tampering.

All medicinal products need to be protected and “consequently need to be packaged in containers that conform to prescribed standards, particularly with respect to the exclusion of moisture and light and the prevention of leaching of extractable substances into the contents and of chemical interaction with the contents. However, the limits of acceptability in these various respects depend, at least in part, on climatic variables. Recommendations in *The international pharmacopoeia* can only be advisory; precise quantitative standards will have to be locally determined” (2).

The complexity of packaging materials and the highly technological nature of medicinal products is such that manufacturers are confronted with significant problems. Interaction between packaging and such products is possible due to the combination of a multiplicity of container components and active pharmaceutical ingredients, excipients and solvents used in a variety of dosage forms.

The quality of the packaging of pharmaceutical products plays a very important role in the quality of such products. It must:

- protect against all adverse external influences that can alter the properties of the product, e.g. moisture, light, oxygen and temperature variations;
- protect against biological contamination;
- protect against physical damage;
- carry the correct information and identification of the product.

The kind of packaging and the materials used must be chosen in such a way that:

- the packaging itself does not have an adverse effect on the product (e.g. through chemical reactions, leaching of packaging materials or absorption);
- the product does not have an adverse effect on the packaging, changing its properties or affecting its protective function.

The resulting requirements must be met throughout the whole of the intended shelf-life of the product. Given the link between the quality of a pharmaceutical product and the quality of its packaging, pharmaceutical packaging materials and systems must be subject, in principle, to the same quality assurance requirements as pharmaceutical products.

The appropriate system of quality assurance for the manufacture of pharmaceutical products should therefore follow the WHO guidelines for good manufacturing practices (GMP) (1).

The requirements to be met by pharmaceutical packaging and packaging materials as described in compendia (pharmacopoeias) and standards (e.g. those of the International Organization for Standardization (ISO)) must be considered only as general in character. The suitability of packaging or packaging material for any particular requirements and conditions can only be ascertained through detailed packaging and stability studies on the product concerned.

Glossary

The definitions given below apply specifically to the terms used in these guidelines. They may have different meanings in other contexts.

General

bulk product

Any product that has completed all the processing stages up to, but not including, final packaging (1).

containers

A container for pharmaceutical use is an article which holds or is intended to contain and protect a drug and is or may be in direct contact with it. The closure is a part of the container. The container and its closure must not interact physically or chemically with the substance within in any way that would alter its quality. The following terms include general requirements for the permeability of containers (3):

- *Well-closed containers* must protect the contents from extraneous matter or from loss of the substance under normal conditions of handling, shipment or storage.
- *Tightly closed containers* must protect the contents from extraneous matter, from loss of the substance, and from efflorescence, deliquescence or evaporation under normal conditions of handling, shipment or storage. If the container is intended to be opened on several occasions, it must be designed to be airtight after reclosure.

- *Hermetically closed containers* must protect the contents from extraneous matter and from loss of the substance, and be impervious to air or any other gas under normal conditions of handling, shipment or storage.

Substances and dosage forms requiring protection from light should be maintained in a *light-resistant container* that — either by reason of the inherent properties of the material of which it is composed, or because a special coating has been applied to it — shields the contents from the effects of light. Alternatively, the container may be placed inside a suitable light-resistant (opaque) covering and/or stored in a dark place (3).

labels

All finished drug products should be identified by labelling, as required by the national legislation, bearing at least the following information:

- (a) the name of the drug product;
- (b) a list of the active ingredients (if applicable, with the International Nonproprietary Names (INNs)), showing the amount of each present, and a statement of the net contents, e.g. number of dosage units, mass or volume;
- (c) the batch number assigned by the manufacturer;
- (d) the expiry date in an uncoded form;
- (e) any special storage conditions or handling precautions that may be necessary;
- (f) the directions for use, and any warnings and precautions that may be necessary;
- (g) the name and address of the manufacturer or the company or person responsible for placing the product on the market.

marketing authorization (product licence, registration certificate)

A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, information given on the label, product information and shelf-life (1).

materials

A term used to denote starting materials, process aids, intermediates, active pharmaceutical ingredients, packaging and labelling materials.

packaging material

Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Primary packaging materials are those that are in direct contact with the product (1).

packaging process

All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product (1).

production

All operations involved in the preparation of a pharmaceutical product, from receipt of the starting materials, through processing and packaging, to completion of the finished product (1).

quarantine

The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing (1).

Containers for pharmaceuticals¹

ampoule

A container sealed by fusion and to be opened exclusively by breaking. The contents are intended for use on one occasion only.

bag

A container consisting of surfaces, whether or not with a flat bottom, made of flexible material, closed at the bottom and at the sides by sealing; the top may be closed by fusion of the material, depending on the intended use.

blister

A multi-dose container consisting of two layers, of which one is shaped to contain the individual doses. Strips are excluded.

bottle

A container with a more or less pronounced neck and usually a flat bottom.

cartridge

A container, usually cylindrical, suitable for liquid or solid pharmaceutical dosage forms; generally for use in a specially designed apparatus (e.g. a prefilled syringe).

gas cylinder

A container, usually cylindrical, suitable for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature.

¹ Based on a list of terms drawn up in response to a request from the European Commission to revise and replace the guidelines of the Committee for Proprietary Medicinal Preparations (III/3593/91).

injection needle

A hollow needle with a locking device intended for the administration of liquid pharmaceutical dosage forms.

injection syringe

A cylindrical device with a cannula-like nozzle, with or without a fixed needle and a movable piston, used for the administration, usually parenteral, of an accurately measured quantity of a liquid pharmaceutical form. The syringe may be prefilled, and can be for single-dose or multi-dose use.

pressurized container

A container suitable for compressed, liquefied or dissolved gas fitted with a device that, after its actuation, produces a controlled spontaneous release of the contents at atmospheric pressure and room temperature.

single-dose container

A container for single doses of solid, semi-solid or liquid preparations.

strip

A multi-dose container consisting of two layers, usually provided with perforations, suitable for containing single doses of solid or semi-solid preparations. Blisters are excluded.

tube

A container for multi-dose semi-solid pharmaceutical forms consisting of collapsible material; the contents are released via a nozzle by squeezing the package.

vial

A small container for parenteral medicinal products, with a stopper and overseal; the contents are removed after piercing the stopper. Both single-dose and multi-dose types exist.

1. Aspects of packaging

1.1 General considerations

Packaging may be defined as the collection of different components (e.g. bottle, vial, closure, cap, ampoule, blister) which surround the pharmaceutical product from the time of production until its use.

The aspects of packaging to be considered (4) include:

- the functions of packaging;
- the selection of a packaging material;
- the testing of the material selected;
- filling and assembling;

- sterilization;
- storage and stability.

Packaging materials (see section 2) include printed material employed in the packaging of a pharmaceutical product, but not any outer packaging used for transportation or shipment. Examples of the types of materials used are shown in Table 1.

A distinction must be made between primary and secondary packaging components. The primary packaging components (e.g. bottles, vials, closures, blisters) are in direct physical contact with the product, whereas the secondary components are not (e.g. aluminium caps, cardboard boxes). The choice of primary and/or secondary packaging materials will depend on the degree of protection required, compatibility with the contents, the filling method and cost, but also the presentation for over-the-counter (OTC) drugs and the convenience of the packaging for the user (e.g. size, weight, method of opening/ reclosing (if appropriate), legibility of printing).

Table 1
Types of raw materials used in packaging

Types of materials	Uses
Cardboard	Boxes Display units
Paper	Labels Leaflets
Glass	Ampoules Bottles Vials Syringes Cartridges
Plastic	Closures Bottles Bags Tubes Laminates with paper or foil
Metal, e.g. aluminium	Collapsible tubes Rigid cans Foil Needles Gas cylinders Pressurized containers
Rubber	Closures, including plungers

Containers may be referred to as primary or secondary, depending on whether they are for immediate use after production of the finished product or not. Both single-dose and multi-dose containers exist. Containers may be well-closed, tightly closed, hermetically closed or light-resistant, as defined in the glossary (3).

The packaging process, as defined in the glossary, is the process that a bulk material must undergo to become a finished product. The properties and attributes of the product should be as specified by the manufacturer and required by the user. The packaging process consists of the following stages:

- filling and assembling;
- sterilization in the final container, if applicable;
- placing labels on the container;
- storage at the manufacturing and shipping sites.

Packaging documentation (1) includes aspects related to:

- specifications and quality control, including batch records;
- labels, inks and adhesive materials (e.g. glue);
- package inserts for patients.

Apart from primary and secondary packaging, two types of special packaging are currently in use, as follows:

- *Unit-dose packaging.* This packaging guarantees safer medication by reducing medication errors; it is also more practical for the patient. It may be very useful in improving compliance with treatment and may also be useful for less stable products.
- *“Device” packaging.* Packaging with the aid of an administration device is user-friendly and also improves compliance. This type of packaging permits easier administration by means of devices such as prefilled syringes, droppers, transdermal delivery systems, pumps and aerosol sprays. Such devices ensure that the medicinal product is administered correctly and in the right amount.

1.2 Functions of packaging

1.2.1 Containment

The containment of the product is the most fundamental function of packaging for medicinal products. The design of high-quality packaging must take into account both the needs of the product and of the manufacturing and distribution system. This requires the packaging:

- not to leak, nor allow diffusion and permeation of the product;
- to be strong enough to hold the contents when subjected to normal handling;
- not to be altered by the ingredients of the formulation in its final dosage form.

1.2.2 Protection

The packaging must protect the product against all adverse external influences that may affect its quality or potency, such as:

- light
- moisture
- oxygen
- biological contamination
- mechanical damage.

The compatibility of the packaging with the active pharmaceutical ingredients is very important in maintaining the integrity of the product.

Stability. Information on stability is given in the guidelines for stability testing of pharmaceutical products containing well-established drug substances in conventional dosage forms (4).

For primary packaging, it is necessary to know the possible interactions between the container and the contents. Normally, product/ component stability and compatibility are confirmed during the primary research and development stage.

While excluding the effect of external factors on the product, the packaging itself should not interact with it so as to introduce unacceptable changes. There are numerous possibilities of interactions between (primary) packaging materials and pharmaceutical products, such as:

- the release of chemicals from components of the packaging materials;
- the release of visible and/or subvisible particles;
- the absorption or adsorption of pharmaceutical components by the packaging materials;
- chemical reactions between the pharmaceutical product and the packaging materials;
- the degradation of packaging components in contact with the pharmaceutical products;
- the influence of the manufacturing process (e.g. sterilization) on the container.

The active pharmaceutical ingredients should remain within their specification limits over the shelf-life of the pharmaceutical product. The question of whether a packaging will provide the required protection for the pharmaceutical product and the required stability over a certain time period can only be answered by means of real-time stability studies. Such studies must evaluate the changes in the quality of the product, in contact with its packaging, during a period equivalent to its intended shelf-life.

In addition, packaging must meet the following requirements:

- it must preserve the physical properties of all dosage forms and protect them against damage or breakage;
- it must not alter the identity of the product;
- it must preserve the characteristic properties of the product, so that the latter complies with its specifications;
- it must protect the product against undesirable or adulterating chemical, biological or physical entities.

Storage. Packaging materials should be stored in accordance with GMP for storage areas (1; see Appendix 1). The characteristics of the active pharmaceutical ingredients will determine whether different packaging will be needed. For example, the packaging requirements of medicinal products kept at temperatures between 2 and 8 °C may differ from those of products intended for tropical countries or light-sensitive products. If the contents are sterile, sterility must be maintained, including that of any unused remaining product.

The shelf-life and utilization period are always determined in relation to storage conditions and the stability of the active pharmaceutical ingredient.

Normal storage conditions are defined as “storage in dry, well-ventilated premises at temperatures of 15–25 °C or, depending on climatic conditions, up to 30 °C. Extraneous odours, other indications of contamination, and intense light have to be excluded” (5).

1.3 Presentation and information

Packaging is also an essential source of information on medicinal products. Such information is provided by labels and package inserts for patients.

The information provided to the patient may include the following:

- the name of the patient;
- the identification number for dispensing records;
- the name, strength, quantity and physical description or identification of the medicinal product;
- directions for use and cautionary statements, if applicable;
- the storage instructions;

- the date of dispensing and period of use (related to the expiry date);
- the name and address of the dispenser.

1.3.1 Labels

Throughout manufacturing, a succession of specific outer labels are applied to the container of the medicinal product. The level of processing is indicated by the following words:

- quarantine
- storage
- distribution.

Specifications for labels for finished drug products are defined in the WHO guidelines on GMP for pharmaceutical products (1; see Appendix 2).

Written labels on the packaging:

- Permit the identification of each active ingredient by means of its INN, and also give the dosage form and the trade name/trademark. All information concerning the medicinal product, as required by national legislation, must be stated on the packaging.
- Preserve the stability of the medicinal product by giving advice on its storage (4):

After the stability of the product has been evaluated, one of the following recommendations as to storage conditions can be prominently indicated on the label:

- store under normal storage conditions;
- store between 2 and 8 °C (under refrigeration, no freezing);
- store below 8 °C (under refrigeration);
- store between -5 and -20 °C (in a freezer);
- store below -18 °C (in a deep freezer).
- Permit the follow-up of a specific medicinal product by means of the batch number on the labels. It must be possible to follow the route of distribution of a product from the manufacturing process to its administration to the patient with the aim of locating and identifying products that are of potential risk (e.g. blood products, blood-derived products).
- Mask the real identity of the medicinal product in clinical studies. This is extremely important in clinical trials in determining the real efficacy of a medicinal product in blinded studies. If the identity is masked by a code, it must be possible to disclose it at any time in a medical emergency.

National legislation must be followed with regard to the information provided to the patient, as well as the record-keeping and packaging instructions.

1.3.2 Repacking, relabelling and dispensing

In some countries, it is common practice not to dispense drugs in the original packaging, but rather in a personalized manner to each patient. This applies especially to solid oral dosage forms, and involves the “repacking” and “relabelling” of drugs in small quantities. Different drugs may even be included in “customized” medication packages, also referred to as “patient med packs”. The quantities of drugs supplied in this way are usually enough only for a short period of time, i.e. to provide drugs for immediate use. It should be remembered, however, that data obtained in stability studies undertaken by the manufacturer are no longer valid for drugs removed from the original package.

Where repacking and relabelling are necessary, the WHO guidelines on GMP for pharmaceutical products (1) should be followed to avoid any mix-up or contamination of the product, which could place the patients’ safety at risk.

1.3.3 Package inserts for patients (patient information leaflets)

Product information must help patients and other users to understand the medication. The patient package insert, together with the label, provides the patient with key information concerning the proper use of the product, potential adverse drug reactions and interactions, storage conditions and the expiry date.

In OTC medicinal products, the package insert, together with the label, may constitute the only pharmaceutical advice that the patient receives.

1.4 Compliance

Packaging and labelling may help to reinforce the instructions given by the physician or the pharmacist, and improve compliance with drug therapy. In this respect, packaging becomes a compliance aid.

The design of pharmaceutical packaging should be such that the product can easily be administered in a safe manner to the patient. If the patient feels at ease with the packaging and route of administration, the design of the packaging may become a key factor in increasing compliance. This is also an important factor in clinical trials.

1.5 Protection of patients

Packaging must not only increase compliance through its design, but must also protect the patient and indicate the integrity of the product. Packaging equipped with a tamper-evident device protects against incidental and accidental poisoning. To protect children, several child-resistant closures have been developed (see section 2.2.3).

1.6 Detection of counterfeiting

The Forty-first World Health Assembly, after reviewing the report of the Executive Board on the implementation of WHO's revised drug strategy, requested: ". . . governments and pharmaceutical manufacturers to cooperate in the detection and prevention of the increasing incidence of the export or smuggling of falsely labelled, spurious, counterfeited or substandard pharmaceutical preparations" (6).

Several documents (2, 6–9) show that counterfeit pharmaceutical products are in wide circulation. In November 1985, during the WHO Conference of Experts on the Rational Use of Drugs in Nairobi, Kenya, concern was expressed regarding the extent to which counterfeit pharmaceutical products were in circulation in developing countries (10). In view of the importance of this issue, a text has been drafted to provide model provisions to deal with counterfeit drugs (11).

The design of the packaging must therefore contribute to preventing tampering with, or the counterfeiting of, certain medicinal products. Such tamper-evident containers can allow the visual inspection of the medicinal product before use, and this may serve as a first stage in detecting counterfeit drugs.

2. Packaging materials and closures

In accordance with the methods of use and administration of medicinal products, packaging materials, closures and containers vary a great deal and have to meet a wide variety of different requirements. All the routes used for systemic access have demanding requirements, which often can only be met by complex structured and formulated medicinal products. This is particularly true of the new medicinal products that are now appearing, such as those administered via transdermal delivery systems.

To ensure the efficacy of a product during its total shelf-life, pharmaceuticals must be regarded as a combination of the medicinal product itself and the packaging.

2.1 Types of material

Only the most commonly used packaging materials and containers are described here.

2.1.1 Glass

For a large number of pharmaceuticals, including medicinal products for oral and local administration, glass containers are usually the first choice (e.g. bottles for tablets, injection syringes for unit- or multi-dose administration). Different types of glass may be necessary, depending on the characteristics and the intended use of the medicinal products concerned.

Manufacturers should arrange with their suppliers to obtain the appropriate type of glass container for the intended use. Suppliers should provide the raw and packaging materials in conformity with industrial norms. Classifications of types of

glass are given in the European and United States pharmacopoeias, whereas no such classification exists in the Japanese pharmacopoeia.

Glass can be tested for light transmission and hydrolytic resistance. In the Japanese pharmacopoeia, such tests are described only for glass containers for injection, whereas in the European and United States pharmacopoeias they are given for all types of glass containers.

2.1.2 Plastics

Some containers are now being made of plastics; the main use is for bags for parenteral solutions. Plastic containers have several advantages compared with glass containers:

- they are unbreakable
- they are collapsible
- they are light.

The European, Japanese and United States pharmacopoeias all describe materials of the same type, but there are considerable differences in the classification and presentation.

As far as tests are concerned, the three pharmacopoeias are extremely difficult to compare. The European pharmacopoeia is the most detailed and requires tests in relation to the use and routes of administration of the medicinal product. Moreover, the same concept is extended to bulk containers for active ingredients.

2.1.3 Metal

Metal containers are used solely for medicinal products for non-parenteral administration. They include tubes, packs made from foil or blisters, cans, and aerosol and gas cylinders. Aluminium and stainless steel are the metals of choice for both primary and secondary packaging for medicinal products. They have certain advantages and provide excellent tamper-evident containers.

Since metal is strong, impermeable to gases and shatterproof, it is the ideal packaging material for pressurized containers.

Descriptions and tests can be found in the norms and standards of the ISO; these have been established in collaboration with manufacturers. Requirements are not given in pharmacopoeias; the suitability of a particular material for a container is normally established by conducting stability studies in which the material is in contact with the drug in question.

2.2 Closures

Closures used for the purpose of covering drug containers after the filling process should be as inert as possible. They should not give rise to undesired interactions between the

contents and the outside environment, and should provide a complete seal. Besides their protective function, closures must also allow the easy and safe administration of the drug.

Depending on the application, closures may have to be pierced with a needle for intravenous sets. Such closures are made from elastomeric materials (rubbers), while those that cannot be pierced are generally made from plastics such as polyethylene or polypropylene.

Depending on the type of container, closures may have different shapes and sizes, e.g. stoppers for infusion or injection bottles or plungers for prefilled syringes. A special design of stopper may also be required for some pharmaceutical production processes such as lyophilization.

Closures, as primary packaging components, are of critical importance and must be carefully selected. They are an essential component of the container and, as such, an integral part of the drug preparation.

A container type which does not require a removable closure at the time of administration is usually preferred since such a container/ closure system avoids, or at least minimizes, the risk of biological and other contamination as well as tampering.

For parenteral preparations, the combination of glass containers and elastomeric closures, usually secured by an aluminium cap, is widely used. Typical examples are infusion bottles, injection vials and prefilled syringes. The rubber closures used within such a system must be carefully selected in accordance with the intended purpose. Most often, improper rubber closures are the cause of incompatibility between the packaging and the drug.

2.2.1 Rubber closures

Rubber consists of several ingredients, one of which is elastomer. Modern rubber compounds used in packaging pharmaceuticals contain only a limited number of ingredients, which are very difficult to extract. Closures made from such materials generally do not pose any problems, and can be used in contact with a large number of drug preparations.

Rubber closures for pharmaceutical use must meet the relevant requirements of the most important pharmacopoeias (the European, Japanese and United States pharmacopoeias). International standards have also been established (ISO 8871). It should be emphasized that the requirements of pharmacopoeias and standards must be seen as minimal requirements. The suitability of a rubber closure for a given application can only be established by means of stability studies.

2.2.2 Caps or overseals

Caps or overseals are used to secure the rubber closure to the container in order to maintain the integrity of the seal under normal conditions of transport, handling and storage during the intended shelf-life of the product. Such caps are usually made

of aluminium and can be equipped with a plastic top to facilitate opening. Caps also provide evidence of tampering: once opened or removed they cannot be repositioned. This is especially true for caps with a plastic top.

2.2.3 Special types of closure

Demographic trends are causing new problems for packaging designers. Thus while child-resistant closures safeguard children against drug intoxication, opening such packaging may prove difficult for the increasing number of elderly persons in the population.

Tamper-evident closures. Tampering includes three aspects, namely altering, pilfering and falsifying the pharmaceutical product.

To prevent tragic accidents and especially malicious tampering, manufacturers try to create safe packaging and governments continue to update regulations to include new tamper-evident technology. In 1975, the United States Food and Drug Administration issued a regulatory requirement for tamper-evident packaging to be used for ophthalmic preparations, thus ensuring that such preparations remained sterile until their use (12). This regulation specifies that the closures must be sealed in such a manner that the contents cannot be used without destroying the seal. In 1982, a further regulation (13) on tamper-evident packaging for OTC human drug products described such packaging as "having an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred".

The concept of tamper-evident packaging is also found in the "General Notice" and "Requirements" of the United States pharmacopoeia, which stipulate that all OTC drugs must comply with the tamper-evident packaging and labelling requirements of the Food and Drug Administration, unless specifically exempted. Products covered by the regulation include all OTC drugs, toothpaste and topical dermatological products, oral cosmetic liquids, contact lens solutions and tablets.

In May 1992, the Food and Drug Administration (14) listed 11 technologies capable of satisfying the definition of tamper-evident packaging, while a twelfth was added for sealed cartons. The list includes film wrappers, blister packs, bubble packs, heat-shrunk bands or wrappers, paper foil or plastic packs, bottles with inner mouth seals, tape seals, breakable cap-ring systems, sealed tubes or plastic blindend heat-sealed tubes, sealed cartons, aerosol containers and all metal and composite cans.

Child-resistant closures. Tragic accidents involving the drug intoxication of children has led to new legislation making it difficult for drug packaging to be opened by young children, while allowing adults easy access. Such packaging is designated as child-resistant.

Certain protocols for child-resistant packaging were established in the USA in 1966. In 1970, the Poison-Prevention Packaging Act was passed and placed under the jurisdiction of the Food and Drug Administration. This Act was transferred in 1973 to

the Consumer Product Safety Commission, which is responsible for drugs and household substances (15). The use of child-resistant packaging has proved effective in reducing child mortality from intoxication by oral prescription drugs, and it is now recognized worldwide that children must be protected against such intoxication.

The ISO has published an internationally agreed standard test procedure for reclosable child-resistant packaging (16). In Europe several norms have been introduced, which complement the ISO standard (17, 18).

The European Committee for Standardization (CEN) has defined a child-resistant package as one “which makes it difficult for young children to gain access to the contents, but which is not too difficult for adults to use properly in accordance with the requirement of this European standard” (19).

The three most common reclosable child-resistant types of closure are the “press-turn”, the “squeeze-turn” and a combination lock.

To determine whether a packaging is child-resistant, it must be subjected to the ISO test procedure for reclosable child-resistant packaging (14).

Most designs that are child-resistant require two hands to open the closure. Such packaging can cause problems for elderly people, and can even lead to the deliberate purchase of drugs with packaging that is not child-resistant; alternatively, the child-resistant closure may not be replaced on the container. An optional “elderly adult test” has been inserted in the ISO standard to deal with this problem.

3. Quality assurance aspects of packaging

3.1 General considerations

To ensure that patients and consumers receive high-quality drugs, the quality management system must take the following considerations into account if the required quality of packaging is to be obtained:

- the requirements of the national authorities and the relevant legislation
- the product
- the production process
- the manufacturers’ internal policies (safety, marketing, etc.).

Bad packaging which is the result of deficiencies in the quality assurance system for packaging can have serious consequences, and packaging defects can create problems that may result in drug recalls. Such defects may include breakage, and problems relating to printing or inks, or errors on labels and package inserts (patient information leaflets). The use of GMP and quality control will prevent the release of a defective medicinal product.

Packaging processes and equipment need validation/qualification in the same way as any other part of processing within a pharmaceutical facility.

3.2 Quality control

Pharmacopoeial specifications and standards for quality control established by national drug quality control laboratories, as already mentioned, can only be regarded as general in character and must be interpreted as minimum standards. The essential part of quality control is performed by the manufacturer during the development, production, release and post-marketing surveillance of the entire medicinal product, i.e. the finished dosage form in its primary and secondary packaging. As pointed out by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-second meeting (1):

Quality control is the part of GMP concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

In the production chain, quality control for packaging contains several critical points. The basic requirements for quality control are as follows (1):

- (a) Adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting and testing starting materials, packaging materials, and intermediate, bulk and finished products, and where appropriate for monitoring environmental conditions for GMP purposes.
- (b) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department.
- (c) Test methods must be validated.
- (d) Records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated.
- (e) The finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container, and correctly labelled.
- (f) Records must be made of the results of inspecting and testing materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures.

. . . The quality control department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, to evaluate, maintain and store the reference standards for substances, to ensure the correct labelling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in the environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

Tests and assays are normally carried out at room temperature (between 15 and 25 °C, or up to 30 °C in some climatic zones), unless otherwise indicated. *The international pharmacopoeia* gives alternative methods to be used if certain instruments are not available.

3.2.1 Sampling

Sampling is used to check the correctness of the label, packaging material or container reference, as well as in the acceptance of consignments, detecting adulteration of the medicinal product, obtaining a sample for retention, etc.

The sampling procedure must take into account the homogeneity and uniformity of the material so as to ensure that the sample is representative of the entire batch.

The sampling procedure should be described in a written protocol. Further details are given in “Sampling procedure for industrially manufactured pharmaceuticals” (20).

3.2.2 Testing programme

The testing programme for quality control purposes may vary from one manufacturer to another. Quality control tests are intended to check the identity of the material concerned. Complete pharmacopoeial or analogous testing may also be carried out, as may special tests, where necessary.

All written specifications for packaging materials and containers should include the nature, extent and frequency of routine tests. Routine tests vary according to the type of material and its immediate packaging, the use of the product, and the route of administration. Nevertheless, such tests usually include the following (21):

- visual inspection (cleanliness, defects)
- tests to identify the material
- dimensional tests
- physical tests
- chemical tests
- microbiological tests.

3.3 Inspection and audit

Self-inspection is covered in Appendix 3, which is taken from Annex 1 of the thirty-second report of the Committee (1).

3.3.1 Rules

It is extremely important to control the security and quality of packaging. The requirements to be met by packaging for pharmaceutical products are more stringent than those for the packaging of food products, although many similarities exist. The goal of inspection is to ascertain the quality of the products, and especially the quality of the packaging. Items for self-inspection include documentation, storage of starting materials and finished products, validation of programmes, production and in-process controls, calibration of instruments or measurement systems, control of labels, sanitation and hygiene, recall procedures, premises (including personnel facilities), and maintenance of buildings and equipment.

Labels play an important part in the quality of packaging. Packaging and labelling errors in the manufacture of pharmaceutical products are often reported.

3.3.2 Audits of suppliers

Pharmaceutical manufacturers are usually audited or inspected by national or international licensing authorities; the same applies to suppliers of starting materials, active pharmaceutical ingredients, excipients and packaging materials. All suppliers of pharmaceuticals and packaging materials play an important role in the chain of quality assurance of the final medicinal product.

Further details can be found in the twenty-fifth and thirtieth reports of the Committee (2, 22), and “General requirements for dosage forms” in *The international pharmacopoeia* (3).

4. Protection of the environment

The protection of the environment has become increasingly important in many countries in recent years. Greater attention has been paid to the disposal and recycling of waste, and legislation has been introduced in many countries.

4.1 Packaging waste

Pharmaceutical packaging represents a very small percentage of waste, but its disposal can cause problems for the environment. For this reason, the Committee, at its thirty-second meeting (1), decided that:

... Provisions should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials

should be stored in suitably designed, separated, enclosed cupboards, as required by national legislation.

. . . Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

Environmental problems result from the methods used for waste disposal, and will depend on the type of packaging waste concerned. Such waste may include:

- uncontaminated waste (assimilated to domestic waste: paper, cardboard, glass, plastic);
- contaminated waste (paper, cardboard, glass, plastic), e.g. waste that has been in contact with blood, blood-derived products, radioactive products or cytotoxic products.

The method of disposal will therefore vary but should always be in accordance with national legislation. Contaminated packaging is often incinerated. The methods of disposal of uncontaminated packaging are shown in Table 2.

Table 2
Methods of disposal of uncontaminated packaging

Material	Recycling	Landfill	Incineration
Paper, cardboard	+++	++	++
Plastics	++	+	+++
Glass	+++	++	NA
Rubber	+	++	+++
Metal	+++	+	NA

+++: Highly recommended; ++: recommended; +: acceptable; NA: not applicable.

4.2 Waste policies

Waste is created at all stages in the production, supply and use of a pharmaceutical product. At each step, care therefore needs to be taken, either by the manufacturer or the end-user, to protect the environment.

Environmental concerns in the international community have led to certain changes in the conditions for the licensing of medicines (23). Thus an environmental risk

assessment may have to be carried out in some cases in order to identify potential risks to the environment arising from the storage, use and disposal of medicinal products. The medicinal product as a whole may become the subject of the environmental risk assessment so that consideration has to be given not only to the active ingredient but also to the adjuvants/exipients in the formulation, and the primary and secondary packaging.

Another major environmental issue affecting certain types of pharmaceutical products concerns the chlorofluorocarbon (CFC) propellants, and the threat that they represent to the ozone layer (24). A European directive has been published on this subject (25).

In several European countries, manufacturers must dispose of their drug waste, or must pay a specialized company to do so for them, and are encouraged to salvage packaging waste. Faced with this problem, manufacturers and pharmacists have, respectively, introduced new directives and new process policies aimed at:

- *Reducing packaging.* Efforts should be made to reduce the volume and weight of packaging materials, and to eliminate packaging which is not essential for the protection of the contents of medicinal products.
- *Salvaging and recycling packaging.* The use of environmental-friendly packaging needs to be considered, i.e. recyclable or degradable packaging. (Valuable packaging materials, such as aluminium, have been extensively recycled for many years. Recently, paper, glass and plastic materials have joined the list of recyclable packaging materials.) However, materials that have been in contact with toxic or highly potent drugs require special consideration.
- *Eliminating and incinerating packaging.* Some plastic materials cannot be recycled and are therefore incinerated. The burning of polyvinyl chloride (PVC) is controversial since, if combustion is not complete, it causes a potential increase in the levels of dioxin in the environment. Incineration can be recommended if the combustion heat produced by it can also be used for other purposes. Developing countries are often short of incinerators. This method is nevertheless regarded as the best available for the elimination of contaminated packaging.

5. Quality specifications

5.1 Requirements in The international pharmacopoeia

5.1.1 Packaging materials

Monographs for inclusion in Volume 6 of *The international pharmacopoeia* (3) have been proposed for glass containers and rubber closures.

5.1.2 Requirements for dosage form containers

Every pharmaceutical preparation must comply with the labelling requirements laid down in the WHO guidelines on GMP for pharmaceutical products (1).

Tablets. These should be kept in well-closed containers and protected from light, moisture, crushing and mechanical shock. Any special storage conditions should be stated on the label. Tablets should be able to withstand handling, including packaging and transportation, without losing their integrity. Moisture-sensitive forms, such as effervescent tablets, should be stored in tightly closed containers or moisture-proof packs, and may require the use of separate packages containing water-adsorbent agents, such as silica gel.

Additional special recommendations for packaging, storage and transportation are specified in the relevant individual monographs.

For effervescent tablets, the label should state "Not to be swallowed directly".

Capsules. These should be packaged and stored in a manner that protects them from microbial contamination. Capsules should be kept in well-closed containers. They should be protected from light, excessive moisture, or dryness, and should not be subjected to temperatures above 30 °C.

Additional special recommendations for packaging, storage and transportation are specified in the relevant individual monographs.

Parenteral preparations. These are usually supplied in glass ampoules, bottles or vials, plastic bottles or bags, and prefilled syringes, which are coloured in the case of light-sensitive substances.

Except where otherwise indicated in the relevant individual monographs, the containers for parenteral preparations should be made from a material that is sufficiently transparent to permit the visual inspection of the contents. They should not adversely affect the quality of the preparation, allow diffusion of any kind into or across the container, or release foreign substances into the preparation.

Closures for containers for parenteral preparations should be equipped with a firm seal to prevent the entry of microorganisms and other contaminants while permitting the withdrawal of a part or the whole of the contents without removal of the closure. They should not be made of materials that react with the contents, nor should they allow foreign substances to diffuse into the preparation. The elastomers of which the closure is made should be sufficiently firm to allow the passage of a needle with the least possible shedding of particles. Closures for multi-dose containers should be sufficiently elastic to allow the puncture to reseal when the needle is withdrawn and thus protect the contents from airborne contamination. A tamper-evident container is fitted with a device that reveals clearly whether it has ever been opened.

On visual inspection, solutions, reconstituted solutions and intravenous infusions (except dispersions) should be clear and free from visible particulate matter.

Topical semi-solid dosage forms. Containers for these dosage forms should be made from a material that does not adversely affect the quality of the preparation or

allow diffusion of any kind into or across the container into the preparation. Closures for these containers should be of a design that minimizes microbial contamination and be equipped with a device that reveals whether the container has ever been opened.

Containers for topical semi-solid dosage forms should protect the preparation from light, moisture, and damage during handling and transportation. The use of suitable metal or plastic flexible tubes is preferred. Preparations for nasal, aural, vaginal or rectal use should be supplied in containers adapted for the appropriate delivery of the product to the site of application, or should be supplied with a suitable applicator.

Topical semi-solid dosage forms should be kept in well-closed containers. The preparation should maintain its pharmaceutical integrity throughout the shelf-life when stored at the temperature indicated on the label; this should normally not exceed 25 °C. Special storage recommendations or limitations are indicated in the relevant individual monographs.

5.2 Pharmacopoeial requirements for containers in Europe, Japan and the USA

5.2.1 Glass containers

As previously mentioned in section 2.1.1, a classification of types of glass for containers for pharmaceutical products does not exist in the Japanese pharmacopoeia, while those given in the European and United States pharmacopoeias are very similar.

Both the European and United States pharmacopoeias provide specifications for glass containers for injections. The latter publication also gives specific guidance for the packaging, repackaging and dispensing of medicinal products. Both the European and United States pharmacopoeias also provide specifications for light-resistant containers and tightly or well-closed closures for capsules and tablets.

The European pharmacopoeia gives a general account of the requirements for glass containers for pharmaceutical use, together with those specifically applicable to glass containers for human blood and blood products.

5.2.2 Plastic containers

Many different plastics are used for containers for medicinal products and the requirements applicable to them differ greatly in the various pharmacopoeias. It is very difficult to compare the tests described. Other and possibly different requirements may be found in international standards.

5.2.3 Rubber closures

A comparison of the requirements for rubber closures is as difficult as that for plastic containers. The European and Japanese pharmacopoeias contain special requirements for rubber closures intended for containers of aqueous parenteral preparations. The

United States pharmacopoeia describes more generally the use of closures made from elastomers for injection bottles, but does not specify the preparations for which they can be used.

Similarities exist between the tests given in the European, Japanese and United States pharmacopoeias, but international standards also exist which differ considerably from one another.

5.3 International Standards

A list of recent International Standards on packaging is given in Appendix 4.

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Appendix 1

Storage areas¹

1. Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.
2. Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.
3. Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.
4. Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.
5. There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.
6. Segregation should be provided for the storage of rejected, recalled or returned materials or products.
7. Highly active materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.
8. Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labelling, and special attention should be paid to the safe and secure storage of these materials.

¹ Previously published in "Good manufacturing practices for pharmaceutical products". In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirtysecond report. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).

Appendix 2

Labels¹

1. All finished drug products should be identified by labelling, as required by the national legislation, bearing at least the following information:
 - (a) the name of the drug product;
 - (b) a list of the active ingredients (if applicable, with the International Nonproprietary Names), showing the amount of each present, and a statement of the net contents, e.g. number of dosage units, weight or volume;
 - (c) the batch number assigned by the manufacturer;
 - (d) the expiry date in an uncoded form;
 - (e) any special storage conditions or handling precautions that may be necessary;
 - (f) directions for use, and warnings and precautions that may be necessary; and
 - (g) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.

¹ Previously published in "Good manufacturing practices for pharmaceutical products". In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).

Appendix 3

Self-inspection and quality audits¹

1. *Principle.* The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively; all recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

Items for self-inspection

2. Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:
 - (a) personnel
 - (b) premises including personnel facilities
 - (c) maintenance of buildings and equipment
 - (d) storage of starting materials and finished products
 - (e) equipment
 - (f) production and in-process controls
 - (g) quality control
 - (h) documentation
 - (i) sanitation and hygiene
 - (j) validation and revalidation programmes
 - (k) calibration of instruments or measurements systems
 - (l) recall procedures
 - (m) complaints management

¹ Previously published in "Good manufacturing practices for pharmaceutical products". In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirtysecond report*. Geneva, World Health Organization, 1992, Annex 1 (WHO Technical Report Series, No. 823).

- (n) labels control
- (o) results of previous self-inspections and any corrective steps taken.

Self-inspection team

- 3. Management should appoint a self-inspection team from local staff who are expert in their own fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of self-inspection

- 4. The frequency at which self-inspections are conducted may depend on company requirements.

Self-inspection report

- 5. A report should be made at the completion of a self-inspection. The report should include:
 - (a) self-inspection results
 - (b) evaluation and conclusions
 - (c) recommended corrective actions.

Follow-up action

- 6. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality audit

- 7. It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors.

Suppliers' audits

- 8. The quality control department should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.
- 9. Before suppliers are approved and included in the specifications they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If the audit is required, it should determine the supplier's ability to conform with GMP standards for active pharmaceutical ingredients.

Appendix 4

International standards on packaging

A list is given below of the standards on packaging issued by the International Organization for Standardization (ISO), as of 10 October 1998, starting with the four main standards, after which they are listed in numerical order.

Quality systems — model for quality assurance in design, development, production, installation and servicing. International Standard ISO 9001. 1994.

Quality systems — model for quality assurance in production, installation and servicing. International Standard ISO 9002. 1994.

Quality systems — model for quality assurance in final inspection and test. International Standard ISO 9003. 1994.

Quality management and quality systems elements. Part 1: Guidelines. International Standard ISO 9004-1. 1994.

Quality management and quality systems elements. Part 2: Guidelines for service. International Standard ISO 9004-2. 1994.

Quality management and quality systems elements. Part 3: Guidelines for processed materials. International Standard ISO 9004-3. 1994.

Quality management and quality systems elements. Part 4: Guidelines for quality improvement. International Standard ISO 9004-4. 1994.

Reusable all-glass or metal-and-glass syringes for medical use. Part 1: Dimensions. International Standard ISO 595-1. 1986.

Reusable all-glass or metal-and-glass syringes for medical use. Part 2: Design, performance requirements and tests. International Standard ISO 595-2. 1987.

Transfusion equipment for medical use. Part 1: Glass transfusion bottles, closures and caps. International Standard ISO 1135-1. 1987.

Plastics collapsible containers for human blood and blood components. International Standard ISO 3826. 1993.

Injection containers for injectables and accessories. Part 1: Injection vials made of glass tubing. International Standard ISO 8362-1. 1989.

Injection containers for injectables and accessories. Part 2: Closures for injection vials. International Standard ISO 8362-2. 1988.

Injection containers for injectables and accessories. Part 3: Aluminium caps for injection vials. International Standard ISO 8362-3. 1989.

Injection containers for injectables and accessories. Part 4: Injection vials made of moulded glass. International Standard ISO 8362-4. 1989.

Injection containers for injectables and accessories. Part 5: Freeze-drying closures for injection vials. International Standard ISO 8362-5. 1995.

Injection containers for injectables and accessories. Part 6: Caps made of aluminium-plastics combinations for injection vials. International Standard ISO 8362-6. 1992.

Injection containers for injectables and accessories. Part 7: Injection caps made of aluminium-plastics combinations without overlapping plastics part. International Standard ISO 8362-7. 1995.

Infusion equipment for medical use. Part 4: Infusion sets for single use, gravity feed. International Standard ISO 8536-4. 1998.

Infusion equipment for medical use. Part 5: Burette-type infusion sets. International Standard ISO 8536-5. 1992.

Infusion equipment for medical use. Part 6: Freeze-drying closures for infusion bottles. International Standard ISO 8536-6. 1995.

Infusion equipment for medical use. Part 7: Caps made of aluminium-plastics combinations for infusion bottles. International Standard ISO 8536-7. 1992.

Sterile single-use syringes, with or without needle, for insulin. International Standard ISO 8537. 1991.

Elastomeric parts for aqueous parenteral preparations. International Standard ISO 8871. 1990.

Aluminium caps for transfusion, infusion and injection bottles — general requirements and test methods. International Standard ISO 8872. 1988.

Injection equipment for medical use. Part 1: Ampoules for injectables. International Standard ISO 9187-1. 2000.

Injection equipment for medical use. Part 2: One-point-cut (OPC) ampoules. International Standard ISO 9187-2. 1993.

Dental cartridge syringes. International Standard ISO 9997. 1999.

Caps made of aluminium-plastics combinations for infusion bottles and injection vials — requirements and test methods. International Standard ISO 10985. 1999.

Prefilled syringes. Part 1: Glass cylinders for dental local anaesthetic cartridges. International Standard ISO 11040-1. 1992.

Prefilled syringes. Part 2: Plungers and discs for dental local anaesthetic cartridges. International Standard ISO 11040-2. 1994.

Prefilled syringes. Part 3: Aluminium caps for dental local anaesthetic cartridges. International Standard ISO 11040-3. 1993.

Prefilled syringes. Part 4: Glass barrels for injectables. International Standard ISO 11040-4. 1996.

Prefilled syringes. Part 5: Plungers for injectables. International Standard ISO 11040-5. 1996.

Containers and accessories for pharmaceutical preparations. Part 1: Drop-dispensing bottles. International Standard ISO 11418-1. 1996.

Containers and accessories for pharmaceutical preparations. Part 2: Screw-neck bottles for syrups. International Standard ISO 11418-2. 1996.

Containers and accessories for pharmaceutical preparations. Part 3: Screw-neck bottles (vials) for solid and liquid dosage forms. International Standard ISO 11418-3. 1996.

Containers and accessories for pharmaceutical preparations. Part 4: Tablet bottles. International Standard ISO 11418-4. 1996.

Containers and accessories for pharmaceutical preparations. Part 5: Dropper assemblies. International Standard ISO 11418-5. 1997.

Containers and accessories for pharmaceutical preparations. Part 7: Screw-neck vials made of glass tubing for liquid dosage forms. International Standard ISO 11418-7. 1998.

Pen-injectors for medical use. Part 1: Requirements and test methods. International Standard ISO 11608-1. 2000.

Pen-injectors for medical use. Part 2: Needles — requirements and test methods. International Standard ISO 11608-2. 2000.

Pen-injectors for medical use. Part 3: Finished cartridges — requirements and test methods. International Standard ISO 11608-3. 2000.

Pen systems. Part 1: Glass cylinders for pen-injectors for medical use. International Standard ISO 13926-1. 1998.

Pen systems. Part 2: Plungers and discs for pen-injectors for medical use. International Standard ISO 13926-2. 1999.

Disposable hanging devices for transfusion and infusion bottles — requirements and test methods. International Standard ISO 15010. 1998.

4.12 Guidelines on the implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce

Annex 9, WHO Technical Report Series, 1033,
2021 (revised)

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1. Introduction

The World Health Organization (WHO) Certification Scheme on the quality of pharmaceutical products moving in international commerce (hereinafter referred to as the “Scheme”) is an international voluntary agreement to provide assurance to countries participating in the Scheme about the quality of pharmaceutical products moving in international commerce. The primary document of the Scheme is the certificate of a pharmaceutical product (CPP).

2. Background

The Scheme has been in operation since 1969 (World Health Assembly resolution WHA 22.50) and was amended in 1975 (WHA 28.65), 1988 (WHA 41.18), 1992 (WHA 45.29) and 1997 (WHA 50.3) (1–5). In 2007, the Forty-second ECSPP discussed and identified a number of perceived problems with the operation of the Scheme (6).

In 2008, a WHO consultation was held to make recommendations for consideration during the Forty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), taking into account the WHO working document QAS/07.240 which contains key issues and possible action (7). The report of the consultation was the working document QAS/08.279 (8). In light of the changing environment, including the rapid globalization of the pharmaceutical manufacturing sector, coupled with changes in the make-up of both the regulators and the groups involved in procurement, the Forty-third ECSPP endorsed the following recommendations (9):

- “1. The *WHO Certification Scheme on the quality of Pharmaceutical products moving in international commerce* should be revised.
2. The proposal for revision of the Scheme and modification of the guidelines should be discussed by the relevant WHO Governing Bodies – the Executive Board and the World Health Assembly – and in consultation with WHO’s Legal Counsel.
3. In the interim, a question and answer (Q&A) paper should be prepared on the function of the Scheme.”

Based on the above recommendations, as an interim measure, a Q&A document on the function of the Scheme was developed in 2010 and revised in 2015 (10, 11). However, the Scheme has not been revised since 1997.

In 2017, the Fifty-second ECSPP recommended that “the WHO Secretariat should prepare a proposal for revision of the Scheme for public consultation” (12).

The draft working document, which includes the proposed revision of the Scheme, was prepared by the WHO Secretariat and it was discussed during an informal consultation that took place from 19 to 20 May 2018.

The draft working document was circulated twice to the Member States and other interested parties for public consultation to prepare a version of the working document for endorsement by the Fifty-fifth ECSPP in 2020.

During the revision process, consideration was given to including reference to the Global Benchmarking Tool (GBT) (13) and the concept of WHO Listed Authorities (14). However, it was considered that since the GBT details are still under discussion, it was too early to add it in the Scheme. Additional wording was instead added to section 4.2 indicating that a Member State or a regional authority should possess an effective marketing authorization, vigilance and market surveillance and control systems for pharmaceutical products.

3. Provisions and objectives

- 3.1 A comprehensive system of certification must be founded on a reliable system of marketing authorization and independent analysis of the pharmaceutical product, as well as upon assurance obtained through independent inspection that all manufacturing operations are carried out in conformity with accepted norms, referred to as “good manufacturing practices” (GMP), and also within relevant provisions already approved in the marketing authorization.
- 3.2 In 1969, the Twenty-second World Health Assembly, by resolution WHA22.50, endorsed requirements for *Good practices in the manufacture and quality control of drugs* (15) (referred to henceforth as “GMP as recommended by WHO”). These comprise internationally-recognized and respected standards that all Member States are urged to adopt and to apply. These requirements have since been revised several times.
- 3.3 These standards provide the basis for the Scheme recommended initially in resolution WHA22.50 (15). The Scheme is an administrative instrument that requires each participating Member State or regional authority, upon application by a commercially interested party, to attest to the competent authority of another participating Member State or regional authority that:
 - a specific product is authorized to be placed on the market within its jurisdiction or, if it is not thus authorized, the reason why that authorization has not been accorded;
 - the manufacturing site is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP (16) as recommended by the WHO in accordance with its current publication;
 - the actual status of commercialization of the certified product on the market of the certifying authority, when authorized; and

- all product information submitted, including labelling, is currently authorized by the certifying authority.

Additionally, the Scheme facilitates the exchange of information related to the investigation of serious quality defects reported in product exported in accordance with its provisions, reliance on the results of GMP inspections performed by other authorities, and also on the results of the assessment of the dossier with the requirements of the certifying authorities.

- 3.4 The Scheme, as amended in 1975 (17), 1988 (18), 1992 (19) and 1997 (20), by resolutions WHA28.65, WHA41.18, WHA45.29 and WHA50.3, is applicable to finished dosage forms of pharmaceutical products intended for administration to human beings or to food-producing animals.
- 3.5 Provisions for certification of starting materials (active pharmaceutical ingredients {APIs} and excipients) for exporting purposes are provided in separate guidelines (21).

4. Membership

- 4.1 Any Member State, as well as regional authority that has the legal right to control the regulation of pharmaceutical products, is eligible to participate on a voluntary basis in the Scheme as a requesting authority. In order to participate, a certifying authority should comply, additionally, with the requirements stipulated in section 4.2. Membership can be voluntarily withdrawn at any time by written notification to the Director-General of WHO.
- 4.2 A Member State or a regional authority intending to become a certifying member should possess:
 - an effective marketing authorization, vigilance and market surveillance and control systems for pharmaceutical products, including the responsible manufacturers and licensing of distributors;
 - GMP requirements, consistent with those recommended by WHO in accordance with its current publication, to which all manufacturers of finished pharmaceutical products (FPP) are required to conform;
 - effective controls to monitor the quality of pharmaceutical products registered or manufactured within its country or region, including access to an independent medicine testing laboratory;
 - a pharmaceuticals inspectorate, operating as an arm of the national or regional medicines regulatory authority, and having the technical competence, experience and resources to assess whether or not GMP and other controls are being effectively implemented, and the legal power

- to conduct or to coordinate appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples; and
- an efficient surveillance system, administrative capacity and good regulatory practices compliance to issue the required certificates efficiently, to detect and institute inquiries in the case of complaint, and to expeditiously notify WHO and, when possible, the competent authority in the Member State or region known to have imported a specific product, or publish the information on the website about the product that is associated with a potentially serious quality defect or other hazard in a timely manner.
- 4.3 Membership as a certifying member and/or requesting member should be declared by notifying in writing to the Director-General of the WHO of:
- its willingness to participate in the Scheme as a certifying member and/or a requesting member;
 - any significant reservations it intends to observe relating to this participation;
 - the commitment of implementing the WHO guideline "*WHO Certification scheme on the quality of pharmaceutical products moving in international commerce*", the WHO Model Certificates (WHO template) and provision of the certificates when requested by a requesting member;
 - the name and address (including email address, telephone and website address) of its medicines regulatory authority or other competent authority;
 - the commitment to notify any change of the information submitted related to the certifying and/or requesting member details; and
 - a declaration to comply with the requirements for a certifying member as stipulated in section 4.2.
- 4.4 A consolidated list of information on the notification submitted by Member States and regional authorities in accordance with the provision in sections 4.2 and 4.3 will be available through WHO's official website (*see also section 3.3*).
- 4.5 A Member State or regional authority should inform the WHO of any change of the information notified to the Director-General of the WHO.

5. Requesting a certificate

- 5.1 Two documents, if available by the certifying authority, can be requested within the scope of the Scheme:

- a certificate of a pharmaceutical product (CPP) and;
 - a batch certificate of a pharmaceutical product (*for more details, please see sections 5.14 and 5.15 and the Explanatory notes in Appendix 2*).
- 5.2 The proposed formats for these documents are provided in appendices 1 and 2 of these guidelines. All participating Member States and regional authorities are henceforth urged to adopt these formats without deletion in order to facilitate the harmonization and interpretation of certified information. A CPP with any deleted sections is no longer considered a “CPP”.
- The explanatory notes attached to the two documents referred to above are very important. Whilst they are not part of the document to be certified, they should always be attached to the certificate.
- 5.3 A list of addresses of national and regional authorities participating in the Scheme that are responsible for the registration of pharmaceutical products for human and/or veterinary use, together with details of any reservations they have declared regarding their participation in the Scheme, will be available on the WHO official website as indicated in section 4.4.
- 5.4 Each authority should issue appropriate guidelines to all agents responsible for importing pharmaceutical products for human and/or veterinary use that operate under its jurisdiction, including those responsible for public sector purchases, in order to explain the contribution of certification to the medicine regulatory process and the circumstances in which each of the two types of documents will be required, the requesting information and the methodology to follow.

Certificate of a pharmaceutical product

- 5.5 The certificate of a pharmaceutical product (CPP) (*Appendix 1*), issued by the certifying authority, is intended for use by the requesting authority in two situations:
- when the product in question is under consideration for a marketing authorization that will authorize its importation and sale, including the GMP compliance of the manufacturer and information on the marketing status of a product in the country of the certifying authority; and
 - when administrative action is required to renew, extend, modify or review such a marketing authorization.
- 5.6 The CPP is intended to facilitate the trade of pharmaceutical products. Its use should have an impact for regulatory authorities and regional bodies in terms of quality and time on the assessment of dossiers for the marketing authorization. The Scheme facilitates reliance among the participating authorities and its use will enable a timely access to medicines.

5.7 All requests for CPPs should be channeled through the applicant. The applicant may submit the following information for each product to the certifying authority:

- the marketing authorization number, name and dosage form of the FPP;
- the name and amount of active ingredient(s) per unit dose (International Nonproprietary Name(s) (INN(s)) where such exist(s));
- the name and address of the marketing authorization holder;
- the name and address of the manufacturing site(s);
- the unit formulation (complete quantitative composition including all excipients);
- the product information for health professionals, the Summary of Product Characteristics (SPC), and for the public (patient information leaflets) as approved by the certifying authority; and
- the packaging of the FPP.

The name(s) and address(es) of manufacturing site(s) that could be submitted to the certifying authority are referred to the FPP, bulk finished product, solvent and diluents, quality control of the FPP, batch release, primary and secondary packaging.

5.8 The certificate is a confidential document which may be issued by the certifying authority only with the permission of the applicant or of the marketing authorization holder.

5.9 The certificate is intended to be incorporated into a marketing authorization application to the requesting authority. Once prepared, it is transmitted to the requesting authority through the applicant and, when applicable, the agent in the importing country.

5.10 When any doubt arises about the status or validity of a certificate, the requesting authority should request verification of the validity of the certificate from the certifying authority, as provided for under section 6.7 of these guidelines.

5.11 In the absence of any specific agreement, each certificate will be prepared always in the working language(s) of the certifying authority. Certifying authorities are encouraged to issue bilingual certificates, including English as the second language, if applicable. The applicant will be responsible for providing any certified translation that may be required by the requesting authority.

5.12 Since the preparation of certificates imposes a significant administrative load on certifying authorities, the service may need to be financed by charges levied upon applicants.

5.13 Additional information is not within the scope of the Scheme. The certifying authority is under no obligation to supply additional information.

Batch certificate

- 5.14 A batch certificate of a pharmaceutical product (Appendix 2) refers to an individual batch of a pharmaceutical product and is a vital instrument in the procurement of medicines. The provision of a batch certificate is usually a mandatory element in tender and procurement documents.
- 5.15 A batch certificate is normally issued by the manufacturer and must accompany and provide an attestation concerning the quality and expiry date of a specific batch or consignment of a product that has already obtained marketing authorization in the importing country. The batch certificate shall include all the parameters (attributes), with acceptance criteria, of the release specification of the pharmaceutical product at the time of batch release and the results. In most circumstances, these certificates are issued by the manufacturer to the importing agent (i.e. the marketing authorization holder in the importing country), but they must be made available at the request of – or in the course of any inspection made on behalf of – the competent authority.

Note: the following are examples of statements and certificates issued in connection with the Scheme. These are not considered to be part of the Scheme:

- **Statement of marketing authorization status of pharmaceutical product(s)** – attests only that a marketing authorization has been issued for a specified product, or products, for use in the certifying country or within the jurisdiction of the certifying regional authority. It is intended for use by importing agents when considering bids made in response to an international tender, in which case it should be requested by the agent as a condition of bidding. It is intended only to facilitate the screening and preparation of information.
- **Batch (lot) release certificate** (22, 23) – issued by the competent authority or competent national laboratory in the certifying country or regional authority, and it refers to the results of a batch or several batches which comply with established specifications and provisions to assure the quality, safety and efficacy (QSE) of the concerned vaccines and vaccine's individual components, as well as with WHO's good manufacturing practices (GMP) for pharmaceutical products and biological products.

6. Issuing a certificate

- 6.1 The certifying authority is responsible for assuring the authenticity of the certified data. Certificates should not bear the WHO logo, but a statement should always be included to confirm that the document is issued in the format recommended by WHO.

- 6.2 When manufacture takes place in a country other than that from which the CPP is issued, an attestation relevant to compliance of the manufacture with GMP should still be provided on the basis of inspections undertaken for registration purposes by the same authority or by another authority.
- 6.3 When the applicant is the manufacturer of the finished dosage form, the certifying authority should satisfy, before attesting compliance with GMP, that the applicant:
 - (a) applies identical GMP standards to the production of all batches of pharmaceutical products manufactured within the site, including those destined exclusively for export; and
 - (b) consents, in the event of identification of a quality defect consistent with the criteria set out in section 5.1, to relevant inspection reports being released, in confidence and where possible, to the requesting authority, should the latter so require.
- 6.4 When the applicant is not the manufacturer of the finished dosage form, the certifying authority should similarly satisfy – in so far as it has the authority to inspect the records and relevant activities of the applicant – that it has the applicant's consent to release relevant reports on the same basis, as described in section 6.3 (b) above.
- 6.5 Whenever a product is purchased through an intermediary, or when more than one set of premises has been involved in the manufacture and packaging of a product, the certifying authority should consider whether or not it has received sufficient information to satisfy that those aspects of the manufacture of the product have been undertaken in compliance with GMP as recommended by WHO.
- 6.6 The certifying authority should officially stamp and date any certificates issued or certify using a secure electronic system/electronic certificate (e-certificate). Every effort should be made to ensure that certificates and all annexed documentation are consistent with the version of the marketing authorization operative on the date of issue. Nevertheless, requesting authorities are discouraged to introduce legalization procedures or any form of authentication procedures such as notarization, embassy legalization and apostillation that may cause the undue delay of certificates.
- 6.7 To avert any potential abuse of the Scheme, to frustrate attempts at falsification, to render routine authentication of certificates by an independent authority superfluous, and to enable the certifying authority to maintain comprehensive records of countries to which certificates have been issued, each certificate should identify the requesting authority and be issued in such a way that the authenticity

of the certificate can be verified using appropriate tools, such as, for example, certification and validation using a secure electronic system.

If requested, an identical copy, clearly marked as a duplicate, may be forwarded by the certifying authority without any undue delay, ideally within 20 working days.

- 6.8 The certifying authority should establish a standard time frame for the issuance of certificates, ideally within 30 working days. It should endeavour to issue a certificate within this period, as soon as the applicant submits sufficient documents, as requested in section 5.7.

7. Notifying and investigating a quality defect

- 7.1 Each certifying authority undertakes to investigate any quality defect reported in a product exported in accordance with the provisions of the Scheme, on the understanding that:
- the complaint is transmitted, together with the relevant facts, through the requesting authority;
 - the complaint is considered to be of a serious nature in terms of risk by the latter authority; and
 - the defect, if it appeared after the delivery of the product into the importing country, is not attributable to local climatic or storage conditions.
- 7.2 In case of doubt, a participating national or regional authority may request WHO to assist in identifying an independent quality control laboratory to carry out tests for the purposes of quality control.
- 7.3 Each certifying authority undertakes to inform WHO and, when possible, all national and regional competent authorities of any serious hazard newly associated with a product exported under the provisions of the Scheme or of any criminal abuse of the Scheme, or publish the information on the website about the product. In the case of substandard or falsified pharmaceutical products, the WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products, should be used to send the notification to WHO (24). Upon receipt of such notification, WHO will inform the competent authority as appropriate and/or issue a WHO Medical Product Alert (25).
- 7.4 WHO stands prepared to offer advice should difficulty arise in implementing any aspect of the Scheme or in resolving a complaint, but it cannot be a party to any resulting litigation or arbitration.

References

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4. World Health Assembly resolution WHA45.29 (1992).
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7. Proposal for improvement of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce (working document QAS/07.240).
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9. Forty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations, Geneva (WHO Technical Report Series, No. 953; https://iris.who.int/bitstream/handle/10665/44553/WHO_TRS_953_eng.pdf?sequence=1&isAllowed=y {2009}, untitled (who.int), accessed 2 February 2021).
10. WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce: Question and Answers (Q&A) (QAS/10.374, 2010).
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12. Fifty-second WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 1010; <https://iris.who.int/bitstream/handle/10665/272452/9789241210195-eng.pdf?sequence=1&isAllowed=y> {2018}, WHO | WHO Expert Committee on Specifications for Pharmaceutical Preparations, accessed 2 February 2021).
13. WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems; <https://www.who.int/tools/global-benchmarking-tools>.
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16. WHO good manufacturing practices: Health product and policy standards. Geneva: World Health Organization (<https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/gmp>, accessed 6 February, 2021).
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Appendix 1

Model certificate of a pharmaceutical product

Certificate of a pharmaceutical product

This certificate conforms to the format recommended by the World Health Organization (WHO). It establishes the status of the pharmaceutical product and of the applicant for the certificate by the national certifying authority in the country or within the jurisdiction of the regional certifying authority. It is for a single product only since the manufacturing arrangements and approved information for different dosage forms and different strengths can vary. (*General instructions and explanatory notes are attached.*)

No. of certificate: _____

Certifying country or regional certifying authority: _____

Requesting country(countries) or regional authority(authorities):

1. Basic information

- 1.1 Name: (International Nonproprietary Name (INN)/generic/chemical name); brand name of the pharmaceutical product as it is declared in the marketing authorization certificate and used within the territory of the certifying authority and, if possible, the brand name for the foreign country as declared by the requester, (if different); and, the dosage form of the finished pharmaceutical product (FPP): _____
- _____

- 1.2 Composition: active pharmaceutical ingredient name(s) using if possible, INNs or national nonproprietary names,. Unit formulation (complete quantitative composition including all excipients);^{1:} _____
- _____

1.3 Is this product authorized by the certifying authority to be marketed in the certifying country or within the jurisdiction of the certifying regional authority? Yes/No (*key in as appropriate*).

1.3.1 Are there restrictions of the sale, distribution or administration of the product specified in the marketing authorization? Yes/No (*key in as appropriate*). See attached information if Yes.

1.4 Is this product actually on the market in the certifying country or within the jurisdiction of the certifying regional authority? Yes/No/Unknown (*key in as appropriate*).

Sections 2A and 2B below are mutually exclusive, therefore:

- If the answer to 1.3 above is yes, continue with section 2A and omit section 2B.
- If the answer to 1.3 above is no, omit section 2A and continue with section 2B

2. Information on marketing authorization

2.A Product that is authorized for marketing by the certifying authority.

2.A.1 Number of marketing authorization and date of issue. (*Indicate, when applicable, if the marketing authorization is provisional and the marketing authorization pathway, e.g. abridged, etc*): _____

2.A.2 Marketing authorization holder (name and address): _____

2.A.3 Status of marketing authorization holder (*one of the options of 3.1, if manufacturer, or specify the status as importer or any other*): _____

2.A.4 Is a summary basis for approval appended? Yes/No (*key in as appropriate*). See attached information if answer is Yes.

2.A.5 Is the attached officially approved product information complete and consistent with the marketing authorization (*such as the Summary of Product Characteristics – SPC- or similar*)? Yes/No/Not provided (*key in as appropriate*). See attached information if answer is Yes.

2.A.6 Name and address of applicant for the certificate as provided by the marketing authorization holder, if different: _____

2.A.7 Web-link to the product marketing authorization information (if available)

2.B Product that is not authorized for marketing by the certifying authority.

2.B.1 Applicant for certificate (name and address): _____

2.B.2 Why is marketing authorization lacking?

Not required/Not requested/Under consideration/Refused/Withdrawal for commercial reasons/Withdrawal for sanitary reasons (*key in as appropriate*)

2.B.3 Reason provided by the applicant for not requesting registration.

(a) The product has been developed exclusively for the treatment of conditions (e.g. tropical diseases – not endemic in the exporting country): _____

(b) The product has been reformulated - please specify: _____

(c) Any other reason, please specify: _____

3. Information on manufacturing and inspections

3.1 List of name and address of the manufacturing site(s) and activities:

- a) manufacturing of all steps of the finished pharmaceutical product (FPP);
- b) manufacturing the bulk finished product;
- c) manufacturing of solvent and diluents;
- d) quality control of the FPP;

- e) batch release of the FPP;
- f) primary packaging of the dosage form;
- g) secondary packaging of the product;
- h) other(s) (specify and list in new arrows).

Name of manufacturing site	Address	Activity

- 3.2 Does the certifying authority arrange for periodic inspection of the manufacturing site in which the of the FPP is produced? Yes/No (*key in as appropriate*). If not, proceed to question 4.
- 3.3 Periodicity of routine inspections: _____
- 3.4 Has the manufacturer of the dosage form of the FPP been inspected? Yes/No (*key in as appropriate*). If Yes, when feasible, insert date of inspection(s) (dd/mm/yyyy).
- 3.5 Do the facilities and operations of the manufacturer of the FPP conform to good manufacturing practices (GMP) as recommended by WHO?² Yes/No (*key in as appropriate*).
- 3.6 It is recommended that for products approved, but not manufactured in the country of the certifying authority, the source of information that assures the GMP compliance of the manufacturer(es) is declared.
4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product? Yes/No (*key in as appropriate*)³. If the answer is No, please explain: _____
- _____
- _____
- _____

Address of certifying authority: _____

Telephone number: _____ Website: _____

Email address: _____

Name and job title of authorized person: _____

Validity of the certificate⁴ (optional): _____

Signature: _____

Stamp and date (*electronic whenever possible*): _____

General instructions

Please refer to the guidelines for full instructions on how to complete this form and for information on the implementation of the Scheme.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

- ¹ Details of quantitative composition are preferred but their provision is subject to the agreement of the marketing authorization holder.
- ² The requirements for good practices in the manufacture and quality control of pharmaceutical products referred to in the certificate, are those included in the Thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series, No. 986, 2014, Annex 2 (*WHO Good manufacturing practices for pharmaceutical products: main principles*). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (*WHO Good manufacturing Practices for biological products*, WHO Technical Report Series, No. 996, 2016, Annex 3).
- ³ It is of particular importance when contractors are involved in the manufacture of the product. The applicant should supply the certifying authority with information in order to identify the contracting parties responsible for each stage of manufacture of the finished dosage form and the extent and nature of any controls exercised over each of these parties.
- ⁴ A period of validity can be provided by the authority on the certificate.

Appendix 2

Model batch certificate of pharmaceutical products

Manufacturers/official¹ batch certificate of a pharmaceutical product

This certificate conforms to the format recommended by the World Health Organization (WHO) (*general instructions and explanatory notes are attached*).

1. No. of certificate: _____
2. Importing (requesting) authority: _____
3. Name: (International Nonproprietary Name (INN)/generic/chemical name); brand name of the pharmaceutical product as it is declared in the marketing authorization certificate and, if possible, brand name for the foreign country, if different. _____

- 3.1 Dosage form: _____
- 3.2 Composition: Active pharmaceutical ingredient name(s) using, if possible, International Nonproprietary Names (INNs) or national nonproprietary names. Unit formulation (complete quantitative composition including all excipients): _____

- 3.2.1 Is the composition of the product identical to that registered in the country of export? Yes/No/Not applicable (key in as appropriate)²

If No: please attach the formula (including excipients) of both products.
4. Marketing authorization holder³ (name and address): _____

- 4.1 Marketing authorization number³: _____
- 4.2 Date of issue³: _____

- 4.3 Marketing authorization issued by³: _____
4.4 Certificate of a pharmaceutical product (CPP) number^{3,4}: _____

5. Pharmaceutical product information:

- 5.1 Batch number: _____
5.2 Date of manufacture: _____
5.3 Shelf life (years): _____
5.4 Contents of container: _____
5.5 Nature of primary container: _____
5.6 Nature of secondary container/wrapping: _____
5.7 Specific storage conditions: _____
5.8 Temperature range: _____

6. Quality analysis: _____

- 6.1 What specifications apply to this dosage form? Either specify the pharmacopoeia or append company specifications.⁵ _____

6.1.1 In the case of a product registered by the certifying country or regional authority, have these company specifications⁵ been accepted by the competent authority? Yes/No (*key in as appropriate*)

- 6.2 Does the batch comply with all parts of the above specifications? Yes/No (*key in as appropriate*)

- 6.3 Append certificate of analysis. Identify and explain any discrepancies from specifications.

It is hereby certified that the above declarations are correct and that the results of the analyses and assays on which they are based will be provided on request to the competent authorities in both the importing and exporting countries.

Name and address of authorized person: _____

Validity of the certificate⁶: _____

Telephone number: _____ Website: _____

Email address: _____

Signature of authorized person: _____

Stamp and date (*electronic whenever possible*): _____

General instructions

Please refer to the guidelines for full instructions on how to complete this form and for information on the implementation of the Scheme.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

The certification of individual batches of a pharmaceutical product is only undertaken on an exceptional basis by the competent authority. Even then, it is rarely applied other than to biological products, such as vaccines, blood and plasma derivatives. For other products, the responsibility for any requirement to provide batch certificates rests with the marketing authorization holder in the certifying country or within the jurisdiction of the certifying regional authority. The responsibility to forward certificates to the competent authority in the importing country is most conveniently assigned to the importing agent.

Any inquiries or complaints regarding a batch certificate should always be addressed to the certifying competent authority. A copy should also be sent to the marketing authorization holder.

¹ Strike out whichever does not apply.

² “Not applicable” means that the product is not registered in the country of export.

³ All items under 4 refer to the marketing authorization or the certificate of a pharmaceutical product (CPP) issued in the certifying country or within the jurisdiction of the certifying regional authority.

⁴ This refers to the CPP as recommended by WHO.

⁵ For each of the parameters to be measured, specifications give the values that have been accepted for batch release at the time of product registration.

⁶ The validity of the certificate should not be confused with the expiry period of the batch/lot.

Appendix 3

Glossary

In order to facilitate understanding, this glossary explains terms in the guidelines and/or refers to relevant sections. It is considered as supplementary information and not as being a formal part of the World Health Organization (WHO) Certification Scheme on the quality of pharmaceutical products moving in international commerce (hereinafter referred to as the “Scheme”).

abuse of Scheme. Actions addressed to the falsification of the certificates of the Scheme, its traceability, to issue them by non-authorized authorities or individuals, and any other activity against the authenticity of the certificates.

active pharmaceutical ingredient (API). Any substance or mixture of substances intended to be used in the manufacture of a finished pharmaceutical product (FPP) and that, when used in the production of a pharmaceutical product, becomes an active ingredient of the FPP. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

applicant. The party applying for a certificate of a pharmaceutical product (CPP). This is normally the agent responsible for importing pharmaceutical products, the marketing authorization holder or other commercially-interested party. In all instances, having regard to the commercial confidentiality of certain data, the certifying authority must obtain permission to release these data from the marketing authorization holder or, in the absence of a marketing authorization holder, from the manufacturer.

batch (synonym: lot). A defined quantity of starting material, packaging material or finished pharmaceutical product (FPP) processed in a single process or a series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

batch certificate (synonym: lot certificate). A document containing information, as set out in Appendix 2 of the guidelines for use, will normally be issued for each batch by the manufacturer. Furthermore, exceptionally, a batch certificate may be validated or issued by the competent authority, particularly for vaccines, sera and other biological products.

The batch certificate travels with every major consignment as a vital instrument in the procurement of medicines. The provision of a batch certificate is usually a mandatory element in tender and procurement documents.

batch number (synonym: lot number). A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

bulk product. Any product that has completed all processing stages up to, but not including, final packaging.

certificate of a pharmaceutical product (CPP). A document containing the information as set out in Appendix 1 of the guidelines that is validated and issued for a specific product by the competent authority of the issuing country or regional authority and intended for use by the competent authority in the importing country/region or, in the absence of such an authority, by the procurement agency.

certifying authority. This is the competent authority in the Member State and regional authority that issues certificates. It shall ensure that it possesses the capacities listed in section 4.2 of the guidelines.

charges for CPPs. Charges levied upon applicants for the issue of a CPP to be paid to the certifying authority due to the significant administrative load imposed to these authorities during the service of preparation of certificates.

competent authority. This is the national or regional authority, as identified in the formal notification to the WHO Director-General, in which each Member State or regional authority informs WHO of its intention to participate in the Scheme. The competent authority can issue or receive certificates. The extent of participation should be indicated in the notification to the WHO Director-General as stipulated in section 4.3 of the guidelines. WHO makes available a continuously updated list of addresses of competent authorities and the specific conditions for participation (*see section 4.4 of the guideline*).

dosage form (synonym: pharmaceutical form). The form of the completed pharmaceutical product (e.g. tablet, capsule, elixir, suppository).

expiry date. The date given on the individual container (usually found on the label) of a pharmaceutical product up to and including the date on which the product is expected to remain within specifications, if stored correctly. It is established for each batch by adding the shelf life to the date of manufacture.

falsified pharmaceutical product. A pharmaceutical product that deliberately or fraudulently misrepresents their identity, composition or source. Any consideration

related to intellectual property rights does not fall within this definition. Such deliberate or fraudulent misrepresentation refers to any substitution, adulteration, reproduction of an authorized pharmaceutical product or the manufacture of a pharmaceutical product that is not an authorized product.

“Identity” shall refer to the name, labelling or packaging or to documents that support the authenticity of an authorized pharmaceutical product.

“Composition” shall refer to any ingredient or component of the pharmaceutical product in accordance with applicable specifications authorized/recognized by a national or regional regulatory authority (NRRA).

“Source” shall refer to the identification, name and address of the marketing authorization holder, manufacturer, importer, exporter, distributor or retailer, as applicable.

A “pharmaceutical product” should not be considered as falsified solely on the grounds that they are unauthorized for marketing in any given country.

finished pharmaceutical product (FPP). A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

good manufacturing practices (GMP). That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

importer. An individual or company or similar legal entity importing or seeking to import a medical product. A “licensed” or “registered” importer is one who has been granted a licence for such purpose.

importing agents, guidelines for. Guidelines on import procedures for pharmaceutical products issued for certifying authorities to all agents responsible for importing pharmaceutical products for human and/or veterinary use that operate under its jurisdiction, including those responsible for public sector purchases, to explain the contribution of certification to the medicine regulatory process and the circumstances in which each of the three types of documents will be required.

intermediaries. Intermediaries in the purchasing of pharmaceutical products for human use. Within the scope of the Scheme, they are responsible for supplying sufficient information to the national or regional certifying authorities to satisfy that those aspects of the manufacture of the product, for which the applicant is not directly responsible, have been undertaken in compliance with good manufacturing practice (GMP) as recommended by WHO.

international nonproprietary name (INN). The shortened scientific name based on the active ingredient. WHO is responsible for assigning INNs to pharmaceutical substances.

manufacture. All operations of the purchase of materials and products, production, quality control, release, storage, distribution of pharmaceutical products and related controls.

manufacturer. A company that carries out operations such as the production, packaging, repackaging, labelling and relabelling of the finished pharmaceutical product and the issuing of the certification.

marketing authorization. A legal document issued by the competent medicines regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality. It must set out, *inter alia*, the name of the product, the pharmaceutical dosage form, the quantitative formula (including excipients) per unit dose (using International Nonproprietary Names (INNs) or national generic names where they exist), the shelf life and storage conditions and packaging characteristics. It specifies the information on which authorization is based (e.g. “The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence.”). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products – the register – and is often said to be “registered” or to “have registration”. Marketing authorization may occasionally also be referred to as a “licence” or “product licence”.

marketing authorization holder. An individual or a corporate entity being in possession of a marketing authorization of a pharmaceutical product.

medicines regulatory authority. A national or regional body that administers the full spectrum of medicine regulatory activities, including at least all of the following functions in conformity with national or regional medicine legislation:

- the marketing authorization of new products and variations of existing products;
- quality control laboratory testing;
- the monitoring of adverse drug reactions;
- the provision of information on medicines and the promotion of rational use of medicines;
- good manufacturing practice (GMP) inspections and licensing of manufacturers, wholesalers and distribution channels;

- enforcement operations; and
- the monitoring of drug utilization.

notarization, embassy legalization or apostillation. Processes of authentication or legalization of certificates addressed to avert the potential abuse of the Scheme, to frustrate attempts at falsification, to render routine authentication of certificates by an independent authority superfluous, and to enable the certifying authority to maintain comprehensive records of countries to which specific products have been exported. In addition, this is also for ensuring that certificates and all annexed documentation are consistent with the version of the marketing authorization operative on the date of issue. It is considered enough for that goal that the complete identification of the requesting authority, and the official seal of the certifying authority (or to certify using a secure electronic system/electronic certificate) be stamped on each page. These traditional legal methods are highly discouraged in the context of the Scheme because they have caused undue delays and have not helped to afford the desired objectives.

pharmaceutical product. Any product intended for human use, or veterinary product intended for administration to food-producing animals, presented in its finished dosage form which is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required; products that may be sold to patients without a prescription; biologicals; and vaccines. It does not, however, include medical devices.

product information. This is the approved product information referred to in section 3.7 of the guidelines and item 2.A.4 of the product certificate. It normally consists of information for health professionals and the public (patient information leaflets) as approved by the related medicines regulatory authority and, when available, a data sheet or a summary of product characteristics approved by the medicines regulatory authority.

production. All operations involved in the preparation of a pharmaceutical product, from receipt of materials through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

registration (synonym: marketing authorization). *See marketing authorization.* As a process, it is any statutory system of approval required at national or regional level as a precondition for introducing a pharmaceutical product onto the market. The result of the process could be a certificate of registration or certificate of marketing authorization.

regional authority. A group of countries in the same geographical region to achieve an integrated marketing authorization system. A regional authority that is willing to participate in the Scheme as a certificating member needs to possess a legal authority stipulated in section 2.2 by itself or through its legal framework.

reliance. An act whereby a regulatory authority in one jurisdiction may take into account or give significant weight to work performed by another regulator, or other trusted institution, in reaching its own decision.

requesting authority. This is the competent authority in the Member State and regional authority that requests certificates.

specifications. A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the test described. It establishes the set of criteria to which a material should conform in order to be considered acceptable for its intended use. “Conformance to specification” means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

substandard pharmaceutical product. Also called “out of specification”, these are authorized pharmaceutical products that fail to meet either their quality standards or their specifications, or both. When the authorized manufacturer deliberately fails to meet these quality standards or specifications due to the misrepresentation of identity, composition or source, then the pharmaceutical product should be considered “falsified”.

summary basis of approval. This refers to the document prepared by some medicines regulatory authorities that summarizes the technical basis on which the product has been licensed (*see section 6.5 of the guidelines and Explanatory note 3 of the product certificate contained in Appendix 1*).

summary product characteristics (SPC). Product information as approved by the medicines regulatory authority. The SPC serves as the basis for production of information for health personnel as well as for consumer information on labels and leaflets of medicinal products and for control of advertising (*see also product information*).

References for Appendix 3

1. WHO good manufacturing practices for active pharmaceutical ingredients. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva, World Health Organization; 2010: Annex 2 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y).
2. WHO good storage and distribution practices for medical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva, World Health Organization; 2020: Annex 7 (WHO Technical Report Series, No. 1025; <https://iris.who.int/bitstream/handle/10665/331814/9789240001824-eng.pdf?sequence=1&isAllowed=y>).
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Appendix 4

(Draft) model notification to the Director-General of the World Health Organization

[*Note This Annex 4 is not a part of the “Guidelines on the implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in International commerce”.*]

The Ministry of Health of the Government of _____ (*name of country*) / _____ (*name of regional authority*) would like to inform the Director-General of the World Health Organization (WHO) that _____ (*name of country or regional authority*) would like to participate/continue to participate in the *WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce* (referred to henceforth as the “Scheme”) as a:

- Certifying member
- Requesting member
- Certifying member and requesting member (*choose only one*).

The Ministry of Health of the Government of _____ (*name of country*) / _____ (*name of regional authority*) hereby confirms that the competent authority(ies) mentioned in the Attachment to this Annex 2 is(are) the legally established authority(-ies) to regulate/control pharmaceutical products.

(*Only for certifying members*)

In addition, we hereby declare that our certifying authority(-ies) in the Attachment possess(es):

- an effective marketing authorization system for pharmaceutical products, including the responsible manufacturers and licensing of distributors;
- Good manufacturing practices (GMP) requirements, consistent with those recommended by WHO in accordance with its current publication, to which all manufacturers of finished pharmaceutical products are required to conform;
- effective controls to monitor the quality of pharmaceutical products registered or manufactured within its country or region, including access to an independent quality control laboratory;

- a pharmaceuticals inspectorate, operating as an arm of the national or regional medicines regulatory authority, and having the technical competence, experience and resources to assess whether or not GMP and other controls are being effectively implemented, and the legal power to conduct or to coordinate the appropriate investigations in order to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples;
- an efficient surveillance system, administrative capacity and good regulatory practices compliance to effectively issue the required certificates; to detect and institute inquiries in the case of complaint and to expeditiously notify WHO and, when possible, the competent authority in the Member State or region known to have imported a specific product; or publish the information on the website about the product that is associated with a potentially serious quality defect or other hazard in a timely manner.

The Ministry of Health of the Government of _____ (*name of country*) / _____ (*name of regional authority*) would once more like to express its gratitude to the World Health Organization for this opportunity to participate/continue to participate in the Scheme.

We also confirm that any change of information in the Attachment will be promptly communicated to the WHO Secretariat.

Signature		Date	
Name and title			

[STAMP]

Attachment

Information on certifying/requesting authority(-ies)

<input type="checkbox"/> Certifying authority	<input type="checkbox"/> Requesting authority	<input type="checkbox"/> Certifying and requesting authority
<i>(choose only one)</i>		
Name of the authority		
Address of the authority		
Telephone number		
Email address		
Website address		
Reservation as per section 4.3 of the Scheme for posting on the WHO website (<i>if any</i>)		
Other remarks (<i>if any</i>)		

(Add tables as necessary)

4.13 Good storage and distribution practices for medical products

Annex 7, WHO Technical Report Series, 1025, 2020 (revised)

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1. Introduction

- 1.1 Storage and distribution are important activities in the supply chain management of medical products. Various people and entities may be responsible for the handling, storage and distribution of medical products. Medical products may be subjected to various risks at different stages in the supply chain, for example, purchasing, storage, repackaging, relabelling, transportation and distribution.
- 1.2 Substandard and falsified products are a significant threat to public health and safety. Consequently, it is essential to protect the supply chain against the penetration of such products.
- 1.3 This document sets out steps to assist in fulfilling the responsibilities involved in the different stages within the supply chain and to avoid the introduction of substandard and falsified products into the market. The relevant sections should be considered as particular roles that entities play in the storage and distribution of medical products.
- 1.4 This guideline is intended to be applicable to all entities involved in any aspect of the storage and distribution of medical products, from the premises of the manufacturer of the medical product to his or her agent, or the person dispensing or providing medical products directly to a patient. This includes all entities involved in different stages of the supply chain of medical products; manufacturers and wholesalers, as well as brokers, suppliers, distributors, logistics providers, traders, transport companies and forwarding agents and their employees.
- 1.5 The relevant sections of this guideline should also be considered for implementation by, amongst others, governments, regulatory bodies, international procurement organizations, donor agencies and certifying bodies, as well as all health-care workers.
- 1.6 This guideline can be used as a tool in the prevention of distribution of substandard and falsified products. It should, however, be noted that these are general guidelines that may be adapted to suit the prevailing situations and conditions in individual countries. National or regional guidelines may be developed to meet specific needs and situations in a particular region or country.
- 1.7 To maintain the quality of medical products, every party that is active in the supply chain has to comply with the applicable legislation and regulations. Every activity in the storage and distribution of medical products should be carried out according to the principles of good manufacturing practices (GMP) (1) or applicable standard such as ISO 13485 for medical devices (2); good storage practices (GSP) (3); and good distribution practices (GDP) (4), as applicable.

- 1.8 This guideline does not deal with dispensing to patients, as this is addressed in the *Joint FIP/WHO* (International Pharmaceutical Federation/World Health Organization) *guidelines on good pharmacy practice* (GPP) (5).
- 1.9 This guideline should also be read in conjunction with other WHO guidelines, for example those listed at the end of the document under References and Further reading.

2. Scope

- 2.1 This document lays down guidelines for the storage and distribution of medical products. It is closely linked to other existing guidelines recommended by the WHO Expert Committee on Specifications for Pharmaceutical Preparations, for example those listed at the end of the document under References and Further reading.
- 2.2 Depending on the national and regional legislation, these guidelines may apply equally to pharmaceutical products for human and veterinary use, and other medical products, where applicable.
- 2.3 The document does not specifically cover GMP aspects of finished products in bulk, distribution of labels, or packaging, as these aspects are considered to be covered by other guidelines. The principles for the distribution of starting materials (active pharmaceutical ingredients [APIs] and excipients) are also not covered here. These are laid down in the WHO document *Good trade and distribution practices for pharmaceutical starting materials* (6).

3. Glossary

The definitions given below apply to the terms used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts and documents.

active pharmaceutical ingredient (API). Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used in the production of a drug, becomes an active ingredient of that drug. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

auditing. An independent and objective activity designed to add value and improve an organization's operations by helping it to accomplish its objectives, using a systematic, disciplined approach to evaluate and improve the effectiveness of risk management, control and governance processes.

batch. A defined quantity of pharmaceutical products processed in a single process or series of processes, so that it is expected to be homogeneous.

batch number. A distinctive combination of numbers and/or letters that uniquely identifies a batch, for example, on the labels, its batch records and corresponding certificates of analysis.

broker. A person or organization that arranges transactions in relation to the sale or purchase of medical products that consist of negotiating, independently and on behalf of another legal or natural person, and that do not include physical handling.

consignment. The quantity of medical products supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include pharmaceutical products belonging to more than one batch.

container. The material employed in the packaging of a medical product. Containers include primary, secondary and transportation containers. Containers are referred to as primary if they are intended to be in direct contact with the product. Secondary containers are not intended to be in direct contact with the product.

contamination. The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a starting material, intermediate or pharmaceutical product during handling, production, sampling, packaging or repackaging, storage or transportation.

contract. Business agreement for the supply of goods or performance of work at a specified price; this may include quality elements in the agreement, or in a separate contract.

corrective and preventative actions (CAPA). A system for implementing corrective and preventive actions resulting from an investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings and trends from process performance and product quality monitoring.

cross-contamination. Contamination of a starting material, intermediate product or finished pharmaceutical product or medical product with another starting material or product, during production, storage and transportation.

distribution. The procuring, purchasing, holding, storing, selling, supplying, importing, exporting or movement of medical products, with the exception of dispensing or providing medical products directly to a patient or his or her agent.

excipient. A substance, other than the active ingredient, which has been appropriately evaluated for safety and is included in a drug delivery system, to aid in the processing of the drug delivery system during its manufacture; protect, support or enhance stability,

bioavailability, or patient acceptability; assist in product identification; or enhance any other attribute of the overall safety and effectiveness of the drug during storage or use.

expiry date. The date given on the individual container (usually on the label) of a medical product, up to and including the date on which the product is expected to remain within specifications if stored correctly. It is established for each batch by adding the shelf-life to the date of manufacture.

falsified product. A product that has been deliberately and/or fraudulently misrepresented as to its identity, composition or source. Such deliberate/fraudulent misrepresentation refers to any substitution, adulteration or reproduction of an authorized product, or the manufacture of a product that is not an authorized product.

“Identity” shall refer to the name, labelling or packaging or to documents that support the authenticity of an authorized product. “Composition” shall refer to any ingredient or component of the product in accordance with applicable specifications authorized/recognized by the national regulatory authority (NRA). “Source” shall refer to the identification, including name and address, of the marketing authorization holder, manufacturer, importer, exporter, distributor or retailer, as applicable (7).

first expiry/first out (FEFO). A distribution procedure that ensures that the stock with the earliest expiry date is distributed and/or used before an identical stock item with a later expiry date is distributed and/or used.

forwarding agent. A person or entity engaged in providing, either directly or indirectly, any service concerned with clearing and forwarding operations in any manner to any other person; this includes a consignment agent.

good distribution practices (GDP). That part of quality assurance that ensures that the quality of a medical product is maintained by means of adequate control of the numerous activities that occur during the trade and distribution process, as well as providing a tool to secure the distribution system from falsified, unapproved, illegally imported, stolen, substandard, adulterated and/or misbranded medical products.

good manufacturing practices (GMP). That part of quality assurance that ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

good pharmacy practice (GPP). The practice of pharmacy aimed at providing and promoting the best use of medicines and other health-care services and products by patients and members of the public. It requires that the welfare of the patient is the pharmacist's prime concern at all times.

good practices (GXP). The group of good practice guides governing the preclinical, clinical, manufacture, testing, storage, distribution and post-market activities for

regulated medical products, such as good laboratory practices (GLP), good clinical practices (GCP), good manufacturing practices (GMP), good pharmacy practice (GPP), good distribution practices (GDP) and other good practices.

good storage practices (GSP). That part of quality assurance that ensures that the quality of medical products is maintained by means of adequate control throughout the storage thereof.

heating, ventilation and air conditioning systems. Heating, ventilation and air conditioning, also referred to as environmental control systems.

importation. The act of bringing or causing any goods to be brought into a customs territory (national territory, excluding any free zone).

intermediate product. Partly processed product that must undergo further manufacturing steps before it becomes a bulk finished product.

labelling. The process of identifying a medical product, including the following information, as appropriate: name of the product; active ingredient(s), type and amount; batch number; expiry date; special storage conditions or handling precautions; directions for use, warnings and precautions; and names and addresses of the manufacturer and/or supplier.

manufacture. All operations of purchase of materials and products, production, packaging, labelling, quality control, release, and storage of medical products and the related controls.

marketing authorization. A legal document issued by the NRA for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy, performance (where applicable) and quality. It must set out, inter alia, the name of the product, the pharmaceutical dosage form; the quantitative formula (including excipients) per unit dose (using International Nonproprietary Names or national generic names where they exist); the shelf-life and storage conditions; and packaging characteristics, or other details as required by the product category. It specifies the information on which authorization is based (e.g. “The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence”). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products – the register – and is often said to be “registered” or to “have registration”. Market authorization may occasionally also be referred to as a “licence” or “product licence”.

material. A general term used to denote starting materials (APIs and excipients), reagents, solvents, process aids, intermediates, packaging materials and labelling materials.

medical products. Products including, but not limited to, finished pharmaceutical products, medical devices including in vitro diagnostic medical devices, and vaccines.

packaging material. Any material, including printed material, employed in the packaging of a medical product, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary, according to whether or not they are intended to be in direct contact with the product.

pedigree. A complete record that traces the ownership of, and transactions relating to, a medical product as it is distributed through the supply chain.

pharmaceutical product. Any product intended for human use, or veterinary product intended for administration to food-producing animals, presented in its finished dosage form, which is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required; products that may be sold to patients without a prescription; biologicals; and vaccines. It does not, however, include medical devices.

product recall. A process for withdrawing or removing a medical product from the distribution chain because of defects in the product, complaints of serious adverse reactions to the product and/or concerns that the product is or may be falsified. The recall might be initiated by the manufacturer, importer, wholesaler, distributor or a responsible agency.

production. All operations involved in the preparation of a medical product, from receipt of materials through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

quality assurance. A wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that medical products are of the quality required for their intended use.

quality risk management. A systematic process for the assessment, control, communication and review of risks to the quality of medical products in the supply chain.

quality system. An appropriate infrastructure, encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that a product (or services) will satisfy given requirements for quality.

quarantine. The status of medical products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

retest date. The date when a material should be re-examined to ensure that it is still suitable for use.

sampling. Operations designed to obtain a representative portion of a medical product, based on an appropriate statistical procedure, for a defined purpose, for example, acceptance of consignments or batch release.

self-inspection. An internal procedure followed to evaluate the entity's compliance with GSP and GDP, as well as GXP in all areas of activities, designed to detect any shortcomings and to recommend and implement necessary corrective actions.

shelf-life. The period of time during which a medical product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch.

standard operating procedure (SOP). An authorized written procedure giving instructions for performing operations that are not necessarily specific to a given product but of a more general nature (e.g. equipment operation, maintenance and cleaning, validation, cleaning of premises, environmental control, sampling and inspection).

storage. The storing of medical products up to the point of use.

substandard products. "Substandard" medical products (also called "out of specification") are authorized by NRAs but fail to meet either national or international quality standards or specifications – or, in some cases, both.

supplier. A person or entity engaged in the activity of providing products and/or services.

transit. The period during which medical products are in the process of being carried, conveyed or transported across, over or through a passage or route to reach their destination.

vehicles. Trucks, vans, buses, minibuses, cars, trailers, aircraft, railway carriages, boats and other means that are used to convey medical products.

4. General principles

- 4.1 There should be collaboration between all entities, including governments, customs agencies, law enforcement agencies, regulatory authorities, manufacturers, distributors and entities responsible for the supply of medical products to patients, to ensure the quality and safety of medical products; to prevent the exposure of patients to substandard and falsified products; and to ensure that the integrity of the distribution chain is maintained.

- 4.2 The principles of GSP and GDP should be included in national legislation and guidelines for the storage and distribution of medical products in a country or region, as applicable, as a means of establishing minimum standards. The principles of GSP and GDP are applicable to:
- medical products moving forward in the distribution chain from the manufacturer;
 - medical products that are moving backwards in the chain, for example, as a result of the return or recall thereof; and
 - donations of medical products.

5. Quality management

- 5.1 Entities involved in the storage and distribution of medical products should have a comprehensively designed, documented and correctly implemented quality system that incorporates GSP, GDP, principles of quality risk management and management review.
- 5.2 Senior management has the ultimate responsibility to ensure that an effective quality system is established, resourced, implemented and maintained.
- 5.3 The quality system should ensure that:
- GSP and GDP are adopted and implemented to ensure that the quality of medical products is maintained throughout their shelf-life in the supply chain; and medical products are appropriately procured, stored, distributed and delivered (in compliance with the legislation) to the appropriate recipients (see Section 18.1);
 - operations are clearly specified in written procedures;
 - responsibilities are clearly specified in job descriptions;
 - all risks are identified and necessary, effective controls are implemented;
 - processes are in place to assure the management of outsourced activities;
 - there is a procedure for self-inspection and quality audits;
 - there is a system for quality risk management;
 - there are systems for managing returns, complaints and recalls; and
 - there are systems to manage changes, deviations and corrective and preventive actions (CAPAs).
- 5.4 There should be an authorized, written quality policy describing the overall intentions and requirements regarding quality. This may be reflected in a quality manual.

- 5.5 There should be an appropriate organizational structure. This should be presented in an authorized organizational chart. The responsibility, authority and interrelationships of personnel should be clearly indicated.
- 5.6 Roles and responsibilities should be clearly defined and understood by the individuals concerned, and recorded as written job descriptions.
- 5.7 The quality system should include appropriate procedures, processes and resources.

6. Quality risk management

- 6.1 There should be a system to assess, control, communicate and review risks identified at all stages in the supply chain.
- 6.2 The evaluation of risk should be based on scientific knowledge and experience and ultimately be linked to the protection of the patient.
- 6.3 Appropriate controls should be developed and implemented to address all risks. The effectiveness of the controls implemented should be evaluated at periodic intervals.

7. Management review

- 7.1 There should be a system for periodic management review. The review should include at least:
 - senior management;
 - review of the quality system and its effectiveness by using quality metrics and key performance indicators;
 - identification of opportunities for continual improvement; and
 - follow-up on recommendations from previous management review meetings.
- 7.2 Minutes and related documentation from management review meetings should be available.

8. Complaints

- 8.1 There should be a written procedure for the handling of complaints. In the case of a complaint about the quality of a medical product or its packaging, the original manufacturer and/or marketing authorization holder should be informed as soon as possible.

- 8.2 All complaints should be recorded and appropriately investigated. The root cause should be Identified, and the impact (e.g. on other batches or products) risk-assessed. Appropriate CAPAs should be taken.
- 8.3 Where required, the information should be shared with the NRA and a recall initiated where appropriate.
- 8.4 A distinction should be made between complaints about a medical product or its packaging and those relating to distribution.
- 8.5 The relevant information, such as the results of the investigation of the complaint, should be shared with the relevant entities.
- 8.6 Medical product quality problems and suspected cases of substandard or falsified products identified should be handled according to relevant authorized procedures. The information should be shared with the manufacturer and appropriate national and/or regional regulatory authorities, without delay.

9. Returned goods

- 9.1 Returned medical products should be handled in accordance with authorized procedures.
- 9.2 All returned medical products should be placed in quarantine upon receipt. The status of the goods should be clear. Precautions should be taken to prevent access and distribution until a decision has been taken with regard to their disposition. The particular storage conditions applicable to the medical products should be maintained until their disposition.
- 9.3 Medical products returned should be destroyed unless it is certain that their quality is satisfactory, after they have been critically assessed in accordance with a written and authorized procedure.
- 9.4 The nature of the medical product, any special storage conditions it requires, its condition and history and the time lapse since it was issued, should all be taken into account in this assessment. Where any doubt arises over the quality of the medical product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.
- 9.5 When handling returned goods, the following considerations at least should be taken:
 - a risk-based process should be followed when deciding on the fate of the returned goods. This should include, but not be limited to, the nature of

- the product, storage conditions, condition of the product history, time-lapse since distribution and the manner and condition of transport while being returned;
 - the terms and conditions of the agreement between the parties; and
 - examination of the returned goods, with decisions taken by suitably qualified, experienced and authorized persons.
- 9.6 Where products are rejected, authorized procedures should be followed, including safe transport.
- 9.7 Destruction of products should be done in accordance with international, national and local requirements regarding disposal of such products, and with due consideration to the protection of the environment.
- 9.8 Records of all returned, rejected and destroyed medical products should be kept for a defined period, in accordance with national requirements.

10. Recalls

- 10.1 There should be a written procedure, in compliance with national or regional requirements, to effectively and promptly recall medical products.
- 10.2 The effectiveness of the procedure should be checked annually and updated as necessary.
- 10.3 The original manufacturer and/or marketing authorization holder, or other relevant contract party, should be informed in the event of a recall.
- 10.4 Information on a recall should be shared with the appropriate national or regional regulatory authority.
- 10.5 All recalled products should be secure, segregated, transported and stored under appropriate conditions. These should be clearly labelled as recalled products. The particular storage conditions applicable to the product should be maintained where possible.
- 10.6 All customers and competent authorities of all countries to which a given medical product may have been distributed should be informed promptly of the recall of the product.
- 10.7 All records, including distribution records, should be readily accessible to the designated person(s) responsible for recalls. These records should contain sufficient information on products supplied to customers (e.g. name, address, contact detail, batch numbers, quantities and safety features – including exported products).

- 10.8 The progress of a recall process should be recorded and a final report issued, which includes a reconciliation between delivered and recovered quantities of medical products.

11. Self-inspection

- 11.1 The quality system should include self-inspections. These should be conducted to monitor the implementation, compliance with and effectiveness of SOPs, as well as compliance with regulations, GSP, GDP and other appropriate guidelines.
- 11.2 Self-inspections should be conducted periodically, according to an annual schedule.
- 11.3 The team conducting the inspection should be free from bias and individual members should have appropriate knowledge and experience.
- 11.4 The results of all self-inspections should be recorded. Reports should contain all observations made during the inspection and presented to the relevant personnel and management.
- 11.5 Necessary CAPAs should be taken and their effectiveness should be reviewed within a defined timeframe.

12. Premises

General

- 12.1 Premises should be suitably located, designed, constructed and maintained, to ensure appropriate operations such as receiving, storage, picking, packing and dispatch of medical products.
- 12.2 There should be sufficient space, lighting and ventilation to ensure required segregation, appropriate storage conditions and cleanliness.
- 12.3 Sufficient security should be provided and access should be controlled.
- 12.4 Appropriate controls and segregation should be provided for products requiring specific handling or storage conditions, such as radioactive materials, products containing hazardous substances and products to be stored under controlled temperature and relative humidity conditions.
- 12.5 Where possible, receiving and dispatch bays should be separate, to avoid mix-ups. Bays should protect products from weather conditions.
- 12.6 Activities relating to receiving and dispatch should be done in accordance with authorized procedures. Areas should be suitably equipped for the operations.

- 12.7 Premises should be kept clean. Cleaning equipment and cleaning agents should not become possible sources of contamination.
- 12.8 Premises should be protected from the entry of birds, rodents, insects and other animals. A rodent and pest control programme should be in place.
- 12.9 Toilets, washing, rest and canteen facilities should be separate from areas where products are handled. Food, eating, drinking and smoking should be prohibited in all areas where medical products are stored or handled.

Receiving area

- 12.10 Each incoming delivery should be checked against the relevant documentation, to ensure that the correct product is delivered from the correct supplier. This may include, for example, the purchase order, containers, label description, batch number, expiry date, product and quantity.
- 12.11 The consignment should be examined for uniformity of the containers and, if necessary, should be subdivided according to the supplier's batch number should the delivery comprise more than one batch. Each batch should be dealt with separately.
- 12.12 Each consignment should be carefully checked for possible contamination, tampering and damage. A representative number of containers in a consignment should be sampled and checked according to a written procedure. Any suspect containers or, if necessary, the entire delivery, should be quarantined for further investigation.
- 12.13 Receiving areas should be of sufficient size to allow the cleaning of incoming medical products.
- 12.14 When required, samples of medical products should be taken by appropriately trained and qualified personnel and in strict accordance with a written sampling procedure and sampling plans. Containers from which samples have been taken should be labelled accordingly.
- 12.15 Following sampling, the goods should be subject to quarantine. Batch segregation should be maintained during quarantine and all subsequent storage.
- 12.16 Materials and products requiring transport and storage under controlled conditions of temperature and relative humidity, as applicable, should be handled as a priority. The transportation temperature data, where appropriate, should be reviewed upon receipt, to ensure that the required conditions had been maintained. Where applicable, cold-chain materials and products should be handled according to the approved conditions by the authority, or as recommended by the manufacturer, as appropriate.

- 12.17 Medical products should not be transferred to saleable stock until an authorized release is obtained.
- 12.18 Measures should be taken to ensure that rejected medical products cannot be used. They should be segregated and securely stored while awaiting destruction or return to the supplier.

Storage areas

- 12.19 Precautions should be taken to prevent unauthorized persons from entering storage areas.
- 12.20 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of medical products.
- 12.21 Storage areas should be appropriately designed, constructed, maintained or adapted. They should be kept clean and there should be sufficient space and lighting.
- 12.22 Storage areas should be maintained within acceptable and specified temperature limits. Where the labels show special storage conditions are required (e.g. temperature, relative humidity), these should be provided, controlled, monitored and recorded.
- 12.23 Materials and medical products should be stored off the floor, away from walls and ceilings, protected from direct sunlight and suitably spaced, to permit ventilation, cleaning and inspection. Suitable pallets should be used and kept in a good state of cleanliness and repair.
- 12.24 A written sanitation programme should be available, indicating the frequency of cleaning and the methods to be used to clean the premises and storage areas.
- 12.25 There should be appropriate procedures for the clean-up of any spillage, to ensure complete removal of any risk of contamination.
- 12.26 Where the status is ensured by storage in separate areas, these areas should be clearly marked and their access restricted to authorized personnel. Any system replacing physical separation and labelling or demarcation should provide equivalent security. For example, computerized systems can be used, provided that they are validated to demonstrate security of access (8).
- 12.27 Sampling should be done under controlled conditions and conducted in such a way that there is no risk of contamination or cross-contamination. Adequate cleaning procedures should be followed after sampling.

- 12.28 Certain materials and products, such as highly active and radioactive materials, narcotics and other hazardous, sensitive and/or dangerous materials and products, as well as substances presenting special risks of abuse, fire or explosion (e.g. combustible liquids and solids and pressurized gases), should be stored in a dedicated area that is subject to appropriate additional safety and security measures, and in accordance with national legislation.
- 12.29 Materials and medical products should be handled and stored in such a manner as to prevent contamination, mix-ups and cross-contamination.
- 12.30 Materials and medical products should be stored in conditions that assure that their quality is maintained. Stock should be appropriately rotated. The “first expired/first out” (FEFO) principle should be followed.
- 12.31 Narcotic medical products should be stored in compliance with international conventions, national laws and regulations on narcotics.
- 12.32 Broken or damaged items should be withdrawn from usable stock and separated.
- 12.33 There should be a written procedure for fire control, including prevention of fire, fire detection and fire drills. Fire-detection and firefighting equipment should be available and should be serviced regularly.

Storage conditions

- 12.34 The storage conditions for medical products should be in compliance with their labelling and information provided by the manufacturer.
- 12.35 Heating, ventilation and air conditioning systems should be appropriately designed, installed, qualified and maintained, to ensure that the required storage conditions are upheld (9).
- 12.36 Mapping studies for temperature, and relative humidity where appropriate, should be done, for example in storage areas, refrigerators and freezers (10).
- 12.37 Temperature and relative humidity, as appropriate, should be controlled and monitored at regular intervals. Data should be recorded and the records should be reviewed. The equipment used for monitoring should be calibrated and be suitable for its intended use. All records pertaining to mapping and monitoring should be kept for a suitable period of time and as required by national legislation.

Note: See Appendix 1 for recommended storage conditions.

13. Stock control and rotation

- 13.1 Records of stock levels for all medical products in store should be maintained, in either paper or electronic format. These records should be updated after each operation (e.g. entries, issues, losses, adjustments). These records should be kept for a suitable period of time and as required by national legislation. Periodic stock reconciliation should be performed at defined intervals, by comparing the actual and recorded stock.
- 13.2 The root cause for stock discrepancies should be identified and appropriate CAPAs taken to prevent recurrence.
- 13.3 When damaged containers are received, this should be brought to the attention of the person responsible for quality. Any action taken should be documented. (These containers should not be issued unless the quality of the medical products has been shown to be unaffected.)
- 13.4 All stock should be checked at regular intervals, to identify those items that are close to their retest or expiry date. Appropriate action should be taken, such as removal of these items from useable stock.

14. Equipment

- 14.1 Equipment, including computerized systems, should be suitable for its intended use. All equipment should be appropriately designed, located, installed, qualified and maintained.
- 14.2 Computerized systems should be capable of achieving the desired output and results.
- 14.3 Where electronic commerce (e-commerce) is used, i.e. electronic means for any of the steps, defined procedures and adequate systems should be in place to ensure traceability and confidence in the supply chain and products concerned.
- 14.4 Electronic transactions (including those conducted via the Internet) relating to the distribution of medical products should be performed only by authorized persons, according to defined and authorized access and privileges.
- 14.5 Where GXP systems are used, these should meet the requirements of WHO or other appropriate guidelines on computerized systems (8, 11).

15. Qualification and validation

- 15.1 The scope and extent of qualification, and validation where appropriate, should be determined using documented risk management principles.

- 15.2 Premises, utilities, equipment and instruments, processes and procedures should be considered.
- 15.3 Qualification and validation should be done following procedures and protocols. The results and outcome of the qualification and validation should be recorded in reports. Deviations should be investigated and the completion of the qualification and validation should be concluded and approved.

16. Personnel

- 16.1 There should be an adequate number of personnel.
- 16.2 Personnel should have appropriate educational qualification, experience and training relative to the activities undertaken.
- 16.3 A designated person within the organization, with appropriate qualification and training, should have the defined authority and responsibility for ensuring that a quality management system is implemented and maintained. This person should preferably be independent from the person responsible for operations and should ensure compliance with GSP and GDP.
- 16.4 Personnel should have the authority and resources needed to carry out their duties and to follow the quality systems, as well as to identify and correct deviations from the established procedures.
- 16.5 There should be arrangements in place to ensure that management and personnel are not subjected to commercial, political, financial or other pressures or conflict of interest that may have an adverse effect on the quality of service provided or on the integrity of medical products.
- 16.6 Safety procedures should be in place relating to all relevant personnel and property, environmental protection and product integrity.
- 16.7 Personnel should receive initial and continued training in accordance with a written training programme. The training should cover the requirements of GSP and GDP (as applicable), as well as on-the-job training. Other topics should be included, such as product security, product identification and the detection of falsified products.
- 16.8 Personnel dealing with hazardous products (such as highly active materials, radioactive materials, narcotics and other hazardous, environmentally sensitive and/or dangerous pharmaceutical products, as well as products presenting special risks of abuse, fire or explosion) should be given specific training.

- 16.9 Personnel should be trained in, and observe high levels of, personal hygiene and sanitation.
- 16.10 Records of all training, attendance and assessments should be kept.
- 16.11 Personnel handling products should wear garments suitable for the activities that they perform. Personnel dealing with hazardous pharmaceutical products, including products containing materials that are highly active, toxic, infectious or sensitizing, should be provided with protective garments as necessary.
- 16.12 Appropriate procedures relating to personnel hygiene, relevant to the activities to be carried out, should be established and observed. Such procedures should cover health, hygiene and the clothing of personnel.
- 16.13 Procedures and conditions of employment for employees, including contract and temporary staff, and other personnel having access to medical products, must be designed and implemented to assist in minimizing the possibility of such products coming into the possession of unauthorized persons or entities.
- 16.14 Codes of practice and procedures should be in place to prevent and address situations where persons involved in the storage and distribution of medical products are suspected of, or found to be implicated in, any activities relating to the misappropriation, tampering, diversion or falsification of any product.

17. Documentation

- 17.1 Documentation includes all procedures, records and data, whether in paper or electronic form. Documents should be appropriately designed, completed, reviewed, authorized, distributed and kept as required. Documents should be readily available.
- 17.2 Written procedures should be followed for the preparation, review, approval, use of and control of all documents relating to the policies and activities for the process of storage and distribution of medical products.
- 17.3 Documents should be laid out in an orderly fashion and be easy to complete, review and check. The title, scope, objective and purpose of each document should be clear.
- 17.4 All documents should be completed, signed and dated as required by authorized person(s) and should not be changed without the necessary authorization.
- 17.5 Documentation should be prepared and maintained in accordance with the national legislation and principles of good documentation practices (11).

- 17.6 Records should be accurate, legible, traceable, attributable and unambiguous. Electronic data should be backed-up in accordance with written procedures. Records should be maintained for the back-up and restoration of data.
- 17.7 Procedures for the identification, collection, indexing, retrieval, storage, maintenance, disposal of and access to all applicable documentation should be followed.
- 17.8 Documents should be reviewed regularly and kept up-to-date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version.
- 17.9 All records should be stored and retained using facilities that prevent unauthorized access, modification, damage, deterioration and/or loss of documentation during the entire life-cycle of the record. Records must be readily retrievable.
- 17.10 Comprehensive records should be maintained for all receipts, storage, issues and distribution. The records should include, for example:
 - date (e.g. receipt or dispatch, as appropriate);
 - name and description of the product;
 - quantity received, or supplied;
 - name and address of the supplier and customer;
 - batch number(s);
 - expiry date;
 - suitability of the supplier;
 - qualification of suppliers; and
 - customer qualification.
- 17.11 All containers should be clearly labelled with at least the name of the medical product, batch number, expiry date or retest date, and the specified storage conditions.

18. Activities and operations

- 18.1 All activities and operations should be conducted in accordance with national legislation, GSP, GDP and associated guidelines.
- 18.2 Storage and distribution of medical products should be done by persons authorized to do so, in accordance with national legislation.
- 18.3 Activities and operations should be performed in accordance with documented procedures.

- 18.4 Automated storage and retrieval systems and operations should comply with current GSP, GDP and GXP guidelines, as well as the recommendations in this guideline.

Receipt

- 18.5 Medical products should be procured from appropriately authorized suppliers.
- 18.6 Deliveries should be examined for damage, seal intactness, signs of tampering, labelling, completeness of order and other related aspects (e.g. availability of a certificate of analysis, where applicable), at the time of receiving.
- 18.7 Containers and consignments that do not meet acceptance criteria at the time of receipt should be labelled, kept separate and investigated. This includes suspected falsified products.

Storage

- 18.8 Medical products requiring specific storage conditions, or controlled access (e.g. narcotics), should be processed without delay and stored in accordance with their requirements.
- 18.9 Appropriate controls should be implemented to prevent contamination and/or mix-ups during storage.
- 18.10 Controls and procedures should be in place to prevent and handle spillage and breakage.

Repackaging and relabelling

- 18.11 Repackaging and relabelling of materials and products are not recommended. Where repackaging and relabelling occur, these activities should only be performed by entities appropriately authorized to do so and in compliance with the applicable national, regional and international requirements, and in accordance with GMP.
- 18.12 Procedures should be in place for the controlled disposal of original packaging, to prevent re-use thereof.

Distribution and transport

- 18.13 Medical products should be transported in accordance with the conditions stated on the labels and described by the manufacturer. The risk to the quality of the medical product during transport and distribution should be eliminated or minimized to an acceptable level.

- 18.14 Product, batch and container identity should be maintained at all times.
- 18.15 All labels should remain legible.
- 18.16 Distribution records should be sufficiently detailed to allow for a recall when required.
- 18.17 Drivers of vehicles should be identified and present appropriate documentation to demonstrate that they are authorized to transport medical products.
- 18.18 Vehicles should be suitable for their purpose, with sufficient space and appropriately equipped to protect medical products.
- 18.19 The design and use of vehicles and equipment must aim to minimize the risk of errors and permit effective cleaning and/or maintenance, to avoid contamination, build-up of dust or dirt and/or any adverse effect on the quality of the products.
- 18.20 Where feasible, consideration should be given to adding technology, such as global positioning system (GPS) electronic tracking devices and engine-kill buttons to vehicles, which would enhance the security and traceability of vehicles with products.
- 18.21 Where possible, dedicated vehicles and equipment should be used for medical products. Where non-dedicated vehicles and equipment are used, procedures should be in place to ensure that the quality of the products will not be compromised. Defective vehicles and equipment should not be used. These should either be labelled as such or removed from service.
- 18.22 There should be procedures in place for the operation and maintenance of all vehicles and equipment.
- 18.23 Equipment and materials used for the cleaning of vehicles should not become a source of contamination or have an adverse effect on product quality.
- 18.24 Vehicles used for transportation of medical products should be qualified, where applicable, to demonstrate their capability to maintain the required transport conditions. There should be a maintenance programme for the cooling/heating system.
- 18.25 Appropriate environmental conditions should be maintained, monitored and recorded. All monitoring records should be kept for a defined period of time, as required by national legislation. Records of monitoring data should be made available for inspection by the regulatory or other oversight body.
- 18.26 Instruments used for monitoring conditions, for example, temperature and humidity, within vehicles and containers should be calibrated at regular intervals.

- 18.26 Rejected, recalled and returned products, as well as those suspected as being falsified, should be securely packaged, clearly labelled and accompanied by the appropriate supporting documentation.
- 18.27 Measures should be in place to prevent unauthorized persons from entering and/or tampering with vehicles and/or equipment, as well as to prevent the theft or misappropriation thereof.
- 18.28 Shipment containers should have no adverse effect on the quality of the medical products and should offer adequate protection to materials and these products. Containers should be labelled indicating, for example, handling and storage conditions, precautions, contents and source, and safety symbols, as appropriate.
- 18.29 Special care should be taken when using dry ice and liquid nitrogen in shipment containers, owing to safety issues and possible adverse effects on the quality of medical products.
- 18.30 Written procedures should be available for the handling of damaged and/or broken shipment containers. Particular attention should be paid to those containing potentially toxic and hazardous products.

Dispatch

- 18.31 There should be documented, detailed procedures for the dispatch of products.
- 18.32 Medical products should only be sold and/or distributed to persons or entities that are authorized to acquire such products in accordance with the applicable national legislation and marketing authorization. Written proof of such authorization, or an import permit or equivalent where there is no marketing authorization, must be obtained prior to the distribution of products to such persons or entities.
- 18.33 Dispatch and transportation should be undertaken only after the receipt of a valid order, which should be documented.
- 18.34 Records for the dispatch of products should be prepared and should include information such as, but not limited to:
- date of dispatch;
 - complete business name and address (no acronyms), type of entity responsible for the transportation, telephone number, names of contact persons;
 - status of the addressee (e.g. retail pharmacy, hospital or community clinic);
 - a description of the products, including, for example, name, dosage form and strength (if applicable);

- quantity of the products, i.e. number of containers and quantity per container (if applicable);
 - applicable transport and storage conditions;
 - a unique number to allow identification of the delivery order; and
 - assigned batch number and expiry date (where not possible at dispatch, this information should at least be kept at receipt, to facilitate traceability).
- 18.35 Records of dispatch should contain sufficient information to enable traceability of the product. Such records should facilitate the recall of a batch of a product, if necessary, as well as the investigation of falsified or potentially falsified products. In addition, the assigned batch number and expiry date of products should be recorded at the point of receipt, to facilitate traceability.
- 18.36 Vehicles and containers should be loaded carefully and systematically on a last-in/first-out (LIFO) basis, to save time when unloading, to prevent physical damage and to reduce security risks. Extra care should be taken during loading and unloading of cartons, to avoid damage.
- 18.37 Medical products should not be supplied or received after their expiry date, or so close to the expiry date that this date is likely to be reached before the products are used by the consumer (12).
- 18.38 Medical products and shipment containers should be secured in order to prevent or to provide evidence of unauthorized access. Vehicles and operators should be provided with additional security where necessary, to prevent theft and other misappropriation of products during transportation.
- 18.39 Medical products should be stored and transported in accordance with procedures such that:
- the identity of the product is not lost;
 - the product does not contaminate and is not contaminated by other products;
 - adequate precautions are taken against spillage, breakage, misappropriation and theft; and
 - appropriate environmental conditions are maintained, for example, using cold-chain for thermolabile products.
- 18.40 Written procedures should be in place for investigating and dealing with any failure to comply with storage requirements, for example, temperature deviations. If a deviation has been noticed during transportation, by the person or entity responsible for transportation, this should be reported to the supplier, distributor

and recipient. In cases where the recipient notices the deviation, it should be reported to the distributor.

- 18.41 Transportation of products containing hazardous substances or narcotics and other dependence-producing substances, should be transported in safe, suitably designed, secured containers and vehicles. In addition, the requirements of applicable international agreements and national legislation should be met.
- 18.42 Spillages should be cleaned up as soon as possible, in order to prevent possible contamination, cross-contamination and hazards. Written procedures should be in place for the handling of such occurrences.
- 18.43 Damage to containers and any other event or problem that occurs during transit must be recorded and reported to the relevant department, entity or authority and investigated.
- 18.44 Products in transit must be accompanied by the appropriate documentation.

19. Outsourced activities

- 19.1 Any activity relating to the storage and distribution of a medical product that is delegated to another person or entity should be performed by the appropriately authorized parties, in accordance with national legislation and the terms of a written contract.
- 19.2 There should be a written contract between the entities. The contract should define the responsibilities of each entity (contract giver and contract acceptor) and cover at least the following:
 - compliance with this guideline and the principles of GSP and GDP;
 - the responsibilities of all entities for measures to avoid the entry of substandard and falsified products into the distribution chain;
 - training of personnel;
 - conditions of subcontracting subject to the written approval of the contract giver; and
 - periodic audits.
- 19.3 The contract giver should assess the contract acceptor before entering into the contract, e.g. through on-site audits, documentation and licensing status review.
- 19.4 The contract giver should provide to the contract acceptor all relevant information relating to the material and medical products.

- 19.5 The contract acceptor should have adequate resources (e.g. premises, equipment, personnel, knowledge, experience and vehicles, as appropriate) to carry out the work.
- 19.6 The contract acceptor should refrain from performing any activity that may adversely affect the materials or products handled.

20. Substandard and falsified products

- 20.1 The quality system should include procedures to assist in identifying and handling medical products that are suspected to be substandard and/or falsified.
- 20.2 Where such medical products are identified, the holder of the marketing authorization, the manufacturer and the appropriate national, regional and international regulatory bodies (as appropriate), as well as other relevant competent authorities, should be informed.
- 20.3 Such products should be stored in a secure, segregated area and clearly identified to prevent further distribution or sale. Access should be controlled.
- 20.4 Records should be maintained reflecting the investigations and action taken, such as disposal of the product. Falsified products should not re-enter the market.

21. Inspection of storage and distribution facilities

- 21.1 Storage and distribution facilities should be inspected by inspectors authorized by national legislation. This should be done at determined, periodic intervals.
- 21.2 Inspectors should have appropriate educational qualifications, knowledge and experience (13).
- 21.3 An inspection should normally be conducted by a team of inspectors.
- 21.4 Inspectors should assess compliance with national legislation, GSP, GDP and related guidelines (GXP), as appropriate.
- 21.5 Inspections should cover the premises, equipment, personnel, activities, quality system, qualification and validation and other related aspects, as contained in this guideline.
- 21.6 An inspection report should be prepared and provided to the inspected entity within a defined period of time from the last day of the inspection. Observations may be categorized based on risk assessment.

- 21.7 CAPA for observations listed as non-compliances in the inspection report, with the national legislation and guidelines, should be submitted for review by the inspectors within the defined period, as stated by the inspectors.
- 21.8 Inspections should be closed with a conclusion after the review of the CAPAs.

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Appendix 1

Recommended storage conditions

Note: Appropriate conditions should be provided for medical products during storage and distribution. Conditions should be maintained as stated on their labels (or as described by the manufacturers as applicable) during storage and distribution. Statements such as “store at ambient conditions” should be avoided. Where possible, actual limits should be specified by the manufacturers, such as “store below 25 °C”. See Table A7.1 below.

Table A7.1
Recommended limits for descriptive storage conditions^a

Label description	Recommended limits
Store at controlled room temperature	15 to 25 °C
Store in a cold or cool place	8 to 15 °C
Store in a refrigerator	5 ± 3 °C
Store in a freezer	-20 ± 5 °C
Store in deep freezer	-70 ± 10 °C
Store in a dry place	No more than 60% relative humidity
Protect from moisture	No more than 60% relative humidity
Store under ambient conditions	Store in well-ventilated premises at temperatures of between 15 °C and 30 °C and no more than 60% relative humidity. Extraneous odours, other indications of contamination and intense light must be excluded.
Protect from light	To be maintained in the original manufacturer's light-resistant containers.
Chilled	5 ± 3 °C

^a These limits are recommended values and are based on pharmacopoeia limits and guidelines.

4.14 Good trade and distribution practices for pharmaceutical starting materials

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Introduction

Good manufacturing practices for active pharmaceutical ingredients were published in 2000 by The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), in ICH Q7 (1). Section 17 of this ICH text includes guidelines for agents, brokers, traders, distributors, repackers and relabellers. This section was written based on the outcome of the World Health Organization (WHO) investigation into deaths resulting from the intentional relabelling of industrial grade ethylene glycol as pharmaceutical grade material. This material was subsequently formulated into a paediatric medicine that caused many deaths. Section 17 of this good manufacturing practice (GMP) guide for active pharmaceutical ingredients (APIs) applies to any party other than the original manufacturer which may trade and/or take possession, repack, relabel, manipulate, distribute or store an API or API intermediate. The scope of ICH Q7 does not include excipients.

Following a number of incidents involving diethylene glycol and a World Health Assembly resolution (WHA52.19), WHO published the *Good trade and distribution practices for pharmaceutical starting materials* in 2004 (2). At the time of publication of these guidelines, WHO had not yet adopted the text from ICH Q7 as GMP for APIs. The WHO guidance for excipients (3), published in 1999, did not cover trade and distribution practices for excipients.

In 2010, WHO published *Good manufacturing practices for active pharmaceutical ingredients* (4), which reflect the text from ICH Q7 and include Section 17 of that document, to replace the existing WHO GMP for APIs.¹

The WHO Expert Committee on Specifications for Pharmaceutical Preparations discussed the revision of the *Good trade and distribution practices for pharmaceutical starting materials* at several meetings. The scope of this WHO guidance on *Good trade and distribution practices for pharmaceutical starting materials* is applicable to any ingredient that is used in the manufacture of a medicinal product, including APIs, excipients and any others.

Note: Material deriving from non-pharmaceutical grades, such as food, industrial or technical grades, should not be designated as pharmaceutical grade when it is not produced under the required manufacturing conditions and quality system. For finished pharmaceutical products (FPPs), details can be found in the WHO good distribution practices for pharmaceutical products (5).

¹ It is important to note that any party that engages in repackaging or blending of an API is considered to be a manufacturer and must submit appropriate registration documents for such manufacturing. He or she must also comply with the GMP for APIs as stated in WHO Technical Report Series, No. 957, Annex 2, 2010 (4).

1. Quality management

- 1.1 Within an organization, quality assurance serves as a management tool. In contractual situations, quality assurance also serves to generate confidence in the supplier. There should be a documented quality policy describing the overall intentions and direction of the distributor regarding quality, which should be formally expressed and authorized by management. The quality policy should clearly indicate that the distributor implements and maintains good trade and distribution practices (GTDP) as described in these guidelines, within the organization and its services.
- 1.2 Quality management should include:
 - an appropriate infrastructure or “quality system”, encompassing the organizational structure, procedures, processes and resources. The size, structure and complexity of the distributor and its activities should be taken into consideration when developing or modifying the quality system;
 - an independent quality unit (or designee), which is responsible for all quality-related matters;
 - an appropriate quality risk management (QRM) system to enable a systematic process for the assessment, control, communication and review of risks to the quality of the product. The extent of application of the QRM system should reflect the operations performed;
 - a validation/qualification system to ensure that the resulting product is capable of meeting the requirements for the specified application;
 - systematic actions necessary to ensure adequate confidence that a material (or service) and relevant documentation will satisfy given requirements for quality – the totality of these actions is termed quality assurance;
 - a clear documented procedure for selecting, approving, disqualifying and re-approving suppliers of pharmaceutical starting materials and services;
 - a robust deviation management and change control programme designed to ensure that quality is continually assessed and maintained: these should include a customer notification where appropriate;
 - a system ensuring traceability of products and associated documentation throughout the entire supply chain.
- 1.3 The system should cover for example, but not be limited to, the quality assurance principles in these guidelines.
- 1.4 All parties involved in the manufacture and supply chain must exercise responsibility to ensure the quality and safety of the materials and products, and that they are fit for their intended use in accordance with their specifications.

- 1.5 The responsibilities placed on any one individual should not be so extensive as to present any risk to quality. In the event of a supplier having a limited number of staff, some duties may be delegated or contracted out to designated persons who are appropriately qualified. There should, however, be no gaps or unexplained overlaps related to the application of GTDP for pharmaceutical starting materials as described in these guidelines.
- 1.6 Where electronic commerce (e-commerce) is used, defined procedures and adequate systems should be in place to ensure confidence in the quality of the material and its traceability.
- 1.7 Authorized release procedures should be in place to ensure that when material is released for its intended purpose, it is of an appropriate quality, meets its specifications and is sourced from approved suppliers.
- 1.8 Implementation of QRM principles using appropriate tools such as hazard analysis and critical control point (HACCP); inspection and certification of compliance with an appropriate quality system such as applicable International Organization for Standardization (ISO) series, and recognition of compliance with national and/or regional standards by external bodies is recommended. However, this should not be seen as a substitute for the implementation of these guidelines or for conforming, for example, to pharmaceutical GMP and good storage practices (GSP) requirements, as applicable.
- 1.9 A system should be in place for the performance of regular internal audits with the aim of continuous improvement. The findings of the audit and any corrective and preventive actions taken, including verification of their effectiveness, should be documented and brought to the attention of the responsible management.

2. Organization and personnel

- 2.1 There should be an adequate organizational structure and a sufficient number of personnel should be employed to carry out all the tasks for which the supplier is responsible.
- 2.2 Individual responsibilities should be clearly defined, understood by the individuals concerned and recorded in writing (as job descriptions or in a contract). Certain activities, such as supervision of performance of activities in accordance with local legislation, may require special attention. Personnel should be suitably qualified, trained and authorized to undertake their duties and responsibilities.
- 2.3 All personnel should be aware of the principles of the appropriate guidelines, including but not limited to GTDP.

- 2.4 Personnel should receive initial and continuing training relevant to their tasks. Training should be provided by qualified trainers in accordance with a training programme. The effectiveness of training should be verified where appropriate. Training records should be maintained. All personnel should be motivated to support the establishment and maintenance of quality standards.
- 2.5 Personnel dealing with hazardous materials (such as highly active, toxic, infectious or sensitizing materials) should be given specific training and should be provided with the necessary protective equipment. Documented policies and procedures for the use of personal protective equipment should be followed to decrease exposure of workers working directly with products and those in the immediate environment.
- 2.6 Personnel who may be exposed to materials from open containers should maintain good hygiene, have no open wounds and should wear appropriate protective garments, gloves, masks and goggles.

3. Premises

- 3.1 Premises, including laboratory facilities, must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid contamination, cross-contamination, mix ups, build-up of dust, dirt or waste and, in general, any adverse effect on the quality of materials.
- 3.2 Measures should be in place to prevent unauthorized persons from entering the premises.
- 3.3 Premises should be designed, equipped and maintained so as to afford maximum protection against the entry of insects, rodents or other animals. A pest control programme should be implemented and maintained. Its effectiveness should be monitored.
- 3.4 Suitable supporting facilities and utilities (such as air control, ventilation and lighting) should be in place and appropriate to the activities performed, in order to avoid contamination, cross-contamination and degradation of the material. Utilities that could affect product quality should be identified and monitored.
- 3.5 If sampling of pharmaceutical starting materials is performed, the sampling area should be separate and in a controlled environment. Sampling should only be performed in a storage area if it can be conducted in such a way that there is no risk of contamination or cross-contamination. Adequate cleaning procedures should be in place for the sampling areas.

4. Procurement, warehousing and storage

Note: GSP are applicable in all circumstances in which, and in all areas where, materials are stored.

- 4.1 Materials should be purchased from approved suppliers in accordance with mutually agreed formal specifications.
- 4.2 Actions should be taken to minimize the risk of falsified or non-conforming materials entering the supply chain.
- 4.3 There should be authorized procedures describing the activities relating to the receipt, storage and distribution of materials. Steps should be taken to ensure and document that the arriving consignment is correct and that the products originate from approved suppliers. Deliveries should be examined to check that containers have not been damaged, altered or tampered with, and that closures and security seals are intact.
- 4.4 Storage areas should have sufficient capacity to allow orderly storage of the various categories of materials.
- 4.5 Receipt and dispatch bays should be equipped with the means to protect materials from adverse environmental conditions. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned before storage if appropriate. Upon receipt, material should be segregated until released by the quality unit.
- 4.6 Segregated areas should be provided for the storage of received, quarantined, rejected, recalled and returned material, including materials with damaged packaging. Any system replacing physical segregation, such as electronic segregation based on a computerized system, should provide equivalent security and should be appropriately qualified and validated.
- 4.7 The storage areas should be kept clean and dry.
- 4.8 Segregated areas and materials should be appropriately identified.
- 4.9 The required storage conditions, as specified for the material, should be maintained within acceptable limits at all times during storage. Appropriate checks to confirm that required shipping conditions have been met should be conducted as soon as possible after receipt.

The product should be transferred to appropriate storage facilities immediately after checks to be made in the goods receiving area have been conducted.

- 4.10 Where special storage conditions are required (e.g. particular temperature, humidity or protection from light) these should be provided, monitored and recorded as appropriate.
- 4.11 Highly active materials, narcotics, other dangerous drugs and substances presenting special risks of abuse, fire or explosion should be stored in safe, dedicated and secure areas. In addition and where applicable, international conventions and national legislation are to be adhered to.
- 4.12 Special attention should be given to the design, use, cleaning and maintenance of all equipment for bulk handling and storage, such as tanks and silos.
- 4.13 Products should be packed in such a way as to avoid breakage, contamination, tampering or theft. The packing should be adequate to maintain the quality of the product during transport. If special shipping conditions have to be met they should be defined, provided and controlled. The containers in which products are shipped should be sealed and should clearly indicate the authenticity of the product and its supplier.
- 4.14 Spillages should be cleaned up as soon as possible to prevent possible cross-contamination and hazard.
- 4.15 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, closed containers in enclosed areas, taking into account the relevant national legislation.
- 4.16 A default system should be in place to ensure that those materials due to expire first are sold or distributed first (earliest expiry/first out). Where no expiry dates are specified for the materials, the first in/first out principle should be applied.
- 4.17 A process should be in place to ensure that materials that have reached their expiry or retest date should be withdrawn immediately from saleable stock. Materials with a retest date should be retested according to the appropriate specifications. Materials with an expiry date should not be retested or used after that date.
- 4.18 Stock inventory should be checked regularly, at least for quantity, overall condition and retesting or expiration dates. Any discrepancies should be investigated.
- 4.19 Controls should be in place to ensure that the correct product is picked, packed and distributed. The material should have an appropriate remaining shelf life. All batch numbers should be recorded.
- 4.20 Storage areas should be clean and free from accumulated waste and from vermin. A written sanitation programme should be available, indicating the frequency of cleaning and the methods to be used to clean the premises and storage areas.

5. Equipment

- 5.1 Equipment must be located, designed, constructed, adapted, qualified, used, cleaned and maintained to suit the operations to be carried out. Its layout, design and use should aim to minimize the risk of errors and permit effective cleaning and maintenance so as to avoid cross-contamination, build-up of dust or dirt and any adverse effect on the quality of materials.
- 5.2 Defective equipment should not be used and should either be removed or labelled as defective. Equipment should be disposed of in such a way as to prevent any misuse.
- 5.3 The status of the equipment should be readily identifiable.
- 5.4 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.
- 5.5 All services, piping and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases, liquids and other materials.
- 5.6 Balances and other measuring equipment of an appropriate range and precision should be available and should be calibrated in accordance with a suitable schedule.
- 5.7 Dedicated equipment should be used where appropriate when handling and/or processing pharmaceutical starting materials. Where non-dedicated equipment is used cleaning validation should be performed.
- 5.8 Closed equipment should be used when possible. If open equipment is used, suitable measures should be taken to prevent contamination.
- 5.9 Procedures should be in place for the operation and maintenance of equipment. Lubricants and other materials used on surfaces that come into direct contact with the materials should be of the appropriate grade, e.g. food-grade oil, and should not alter the quality of the materials.
- 5.10 Washing and cleaning equipment should be chosen and used such that it cannot be a source of contamination.

6. Documentation

- 6.1 Documents, in particular instructions and procedures relating to any activity that might have an impact on the quality of materials, should be designed, completed, reviewed and distributed with care. Documents should be completed, approved, signed and dated by appropriate authorized persons and should not be changed

without authorization. Specifications for materials, including packaging materials, should be available, reviewed and revised on a regular basis.

6.2 Documents should have unambiguous contents: their title, nature and purpose should be clearly stated. They should be laid out in an orderly manner and be easy to check.

6.3 Certificates of analysis (COAs) issued by the original manufacturer should be provided. If additional testing is done, all COAs should be provided.

COAs should document product traceability back to the manufacturer by naming the original manufacturer and the manufacturing site. COAs should indicate which results were obtained by testing the original material and which results came from skip-lot testing or other testing and should specify the organization responsible for issuing the COA.

6.4 Before any material is sold or distributed, the supplier should ensure that the COAs and results are available and that the results meet the required specifications.

6.5 The original manufacturer and the intermediaries handling the material should always be traceable and transparent; and this information should be made available to authorities and end-users, downstream and upstream, when requested.

6.6 Depending upon risk assessment, and in accordance with the national requirements, quality agreements should form the basis of the relationship for all parties involved in the supply chain. The agreements should include mechanisms to allow transfer of information, e.g. quality or regulatory information and change control.

6.7 Labels applied to containers should be clear, unambiguous, permanently fixed and should be printed in the company's agreed format. The information on the label should be indelible.

6.8 Each container should be identified by labelling bearing at least the following information:

- the name of the pharmaceutical starting material (including grade and reference to pharmacopoeias where relevant);
- if applicable, the International Nonproprietary Name (INN);
- the amount (weight or volume);
- the batch number assigned by the original manufacturer or the batch number assigned by the repacker, if the material has been repacked and relabelled;
- the retest date or expiry date (where applicable);

- the storage conditions;
- handling precautions, where necessary;
- identification of the original manufacturing site;
- name and contact details of the supplier.

6.9 Relevant storage and handling information and safety data sheets should be available.

6.10 Records should be kept and must be readily available upon request in accordance with GMP and GSP (6).

7. Repackaging and relabelling

7.1 Operations, such as combining into a homogeneous batch, repackaging and/or relabelling, are manufacturing processes and are not recommended. In circumstances where they are to be conducted, their performance should be in compliance with GMP.

Note: It is important to note that any party who engages in repackaging or blending of an API is considered to be a manufacturer and must submit appropriate registration documents for such manufacturing. They must also comply with the GMP for APIs as set out in WHO Technical Report Series, No. 957, Annex 2, 2010 (4).

7.2 Special attention should be given to the following points:

- prevention of contamination, cross-contamination and mix ups;
- appropriate environmental conditions for dispensing, packaging and sampling;
- security of stocks of labels, line clearance checks, online inspections, destruction of excess batch-printed labels and label reconciliation;
- good sanitation and hygiene practices;
- maintaining batch integrity (mixing of different batches of the same solid material should normally not be done);
- as part of batch records, all labels that were removed from the original container during operations, and a sample of the new label, should be kept;
- if more than one batch of labels is used in one operation, samples of each batch should be kept;
- maintaining product identity, integrity and traceability.

7.3 Upon receipt, packaging materials should be placed in quarantine and should not be used prior to release. There should be procedures for the inspection, approval and release of the packaging materials.

- 7.4 When different batches of a material from the same original manufacturing site are received by a distributor and combined into a homogeneous batch, the conformity of each batch with its specification should be confirmed before it is added.
- 7.5 Only materials from the same manufacturing site, received by a distributor and conforming to the same specifications, can be mixed. If different batches of the same material are mixed to form a homogeneous batch it should be defined as a new batch, tested and supplied with a batch certificate of analysis. In such cases the customer should be informed that the material supplied is a mixture of manufacturers' batches.
- 7.6 In all cases, traceability back to the manufacturer should be documented by identifying the original manufacturer of the specific batch of the material and its manufacturing site.
- 7.7 If batches are combined or mixed, the oldest batch should determine the expiry or retest date assigned to the combined or mixed batch.
- 7.8 If the integrity and quality of the batch is maintained during repackaging and relabelling, then the original COA of the original manufacturer should be provided. If retesting is done, both the original and the new COA should be provided as long as the batch integrity is maintained. The batch referred to on the new COA should be traceable to the original COA.
- 7.9 Repackaging of materials should be carried out using approved packaging materials for which the quality and suitability have been established as being equal to or better than those of the original container.
- 7.10 The reuse of containers should be discouraged unless they have been cleaned using a validated procedure. Recycled containers should not be used unless there is evidence that the quality of the material packed in them will not be adversely affected.
- 7.11 Materials should be repackaged only if efficient environmental control exists to ensure that there is no possibility of contamination, cross-contamination, degradation, physicochemical changes and/or mix ups. The quality of air supplied to the area should be suitable for the activities performed, e.g. there should be efficient filtration.
- 7.12 Suitable procedures should be followed to ensure proper label control.
- 7.13 Containers of repackaged material and relabelled containers should bear both the name of the original manufacturing site and the name of the distributor/repacker.

- 7.14 Procedures should be in place to ensure maintenance of the identity and quality of the material by appropriate means, both before and after repackaging operations.
- 7.15 Each batch of repackaged material should be tested to ensure that the material conforms to documented specifications.
- 7.16 There should be a procedure to ensure that appropriate repackaging documentation, in addition to the test results, is evaluated prior to release of the repackaged material.
- 7.17 Sampling, analytical testing and batch release procedures should be in accordance with GMP.
- 7.18 Only official pharmacopoeial methods or validated analytical test methods should be used for the analysis. Where alternatives to the test methods specified in a monograph are used to provide test results, those alternative methods should be demonstrated to be suitable and equivalent.
- 7.19 Out-of-specification test results should be investigated and documented.
- 7.20 Samples of pharmaceutical starting materials in appropriate quantities should be kept for at least one year after the expiry or retest date, or for three years after distribution is complete.
- 7.21 The repacker and relabeller should ensure that the stability of the material is not adversely affected by the repackaging or relabelling. Stability studies to justify assigned expiration or retest dates should be conducted if the pharmaceutical starting material is repackaged in a container different from that used by the original manufacturer. It is recognized that some excipients may not need additional stability studies.

8. Complaints

- 8.1 All complaints and other information concerning potentially defective materials must be carefully reviewed according to written procedures that describe the action to be taken and specify the criteria on which a decision to recall a product should be based. Records of complaints should be retained and evaluated for trends at defined intervals.
- 8.2 Any complaint concerning a material defect should be recorded and thoroughly investigated to identify the origin or reason for the complaint (e.g. the repackaging procedure or the original manufacturing process). Corrective and preventive actions should be taken where appropriate, and recorded.

- 8.3 If a defect in a pharmaceutical starting material is discovered or suspected, consideration should be given to whether other batches should be checked.
- 8.4 Where necessary, appropriate follow-up action, possibly including a recall, should be taken after investigation and evaluation of the complaint.
- 8.5 The manufacturer and customers should be informed if action is needed following possible faulty manufacturing, packaging, deterioration or any other serious quality problems with a pharmaceutical starting material.

9. Recalls

- 9.1 There should be a system for recalling promptly and effectively from the market, materials known or suspected to be defective.
- 9.2 The original manufacturer should be informed in the event of a recall.
- 9.3 There should be detailed written procedures for the organization of any recall activity. These procedure(s) should be regularly reviewed and updated.
- 9.4 All recalled materials should be stored in a secure area while their fate is decided.
- 9.5 In the event of serious or potentially life-threatening situations, all customers and competent authorities in all countries to which a given material may have been distributed should be promptly informed of any intention to recall the material.
- 9.6 All records should be readily available to the designated person(s) responsible for recalls. These records should contain sufficient information on materials supplied to customers (including exported materials).
- 9.7 The effectiveness of the arrangements for recalls should be evaluated at regular intervals.

10. Returned goods

- 10.1 Goods returned to the supplier should be appropriately identified and quarantined. The conditions under which returned goods have been stored and shipped should be evaluated to determine the quality of the returned goods.
- 10.2 The quality unit or designee should decide on the disposition of the returned goods following a formal and documented investigation process. Corrective and preventive actions should be taken where appropriate.

11. Handling of non-conforming materials

- 11.1 Non-conforming materials should be handled in accordance with a procedure that will prevent their introduction or reintroduction into the market. Records covering all activities, including destruction, disposal, return and reclassification, should be maintained.
- 11.2 An investigation should be performed to establish whether any other batches are also affected. Corrective and preventive measures should be taken where necessary.
- 11.3 The disposition of the material, including downgrading to other suitable purposes, should be documented.
- 11.4 Non-conforming materials should never be blended with materials that do comply with specifications.

12. Dispatch and transport

- 12.1 Materials should be loaded, unloaded and transported in a manner that will ensure the maintenance of controlled conditions where applicable (e.g. temperature, protection from the environment). The transport process should not adversely affect the materials. Any carrier used for transport should be approved according to a written procedure unless the carrier has been selected by the customer.
- 12.2 Requirements for special transport and/or storage conditions should be stated on the label and/or in the transport documentation. If the pharmaceutical starting material is intended to be transferred outside the control of the manufacturer's materials management system, the name and address of the manufacturer, quality of contents, special transport conditions and any special legal requirements should also be included on the label and/or in the transport documentation.
- 12.3 The supplier of the materials should ensure that the contract acceptor for transportation of the materials is aware of and provides the appropriate storage and transport conditions, e.g. through audits.
- 12.4 Procedures should be in place to ensure proper cleaning and prevention of cross-contamination when liquids (tanks) and bulk or packed materials are transported.
- 12.5 The bulk transport of pharmaceutical starting materials requires numerous precautions to avoid contamination and cross-contamination. The best practice is to use dedicated equipment, tanks or containers.
- 12.6 Packaging materials and transportation containers should be suitable to prevent damage to the pharmaceutical starting materials during transport.

- 12.7 For bulk transport, validated cleaning procedures should be used between loadings, and a list of restricted previous cargoes must be supplied to the transport companies.
- 12.8 Steps should be taken to prevent unauthorized access to the materials being transported.
- 12.9 General international requirements regarding safety aspects (e.g. prevention of explosion and of contamination of the environment) should be observed.

13. Contract activities

- 13.1 Any activity performed, as referenced in the GMP and GTDP guidelines, delegated to another party, should be agreed upon in a written contract.
- 13.2 The contract giver should evaluate the proposed contract acceptor's compliance with GTDP before entering into an agreement.
- 13.3 All contract acceptors should comply with the requirements in these guidelines. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.
- 13.4 There should be a written and approved contract or formal agreement between the contract giver and contract acceptor that addresses and defines in detail the responsibilities with respect to GTDP and which party is responsible for which quality measures.
- 13.5 Subcontracting may be permissible under certain conditions, subject to approval by the contract giver, especially for activities such as sampling, analysis, repacking and relabelling.

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4.15 Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

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Abbreviations

CAPA	corrective and preventive action (procedures)
DCVMN	Developing Countries Vaccine Manufacturers Network
EEFO	earliest-expiry-first-out. Used in this document as equivalent to FEFO (first to expire-first-out)
FIFO	first-in-first-out
GDP	good distribution practice
GMP	good manufacturing practice
GPS	global positioning system
GSP	good storage practice
HVAC	heating ventilating and air-conditioning (system)
IATA	International Air Transport Association
IFPMA	International Federation of Pharmaceutical Manufacturers and Associations
IQ	installation qualification
PCCIG	Pharmaceutical Cold Chain Interest Group
PDA	Parenteral Drug Association
SKU	stock-keeping unit
SLA	service level agreement
SMS	short message service
SOP	standard operating procedure
TTSPP	time- and temperature-sensitive pharmaceutical product
UPS	uninterrupted power supply
USP	United States Pharmacopeia

Background

These guidelines set out the principal requirements for the safe storage and distribution of time- and temperature-sensitive pharmaceutical products (TTSPPs). They are based upon existing regulations and best practice guidance from a wide range of international sources (see References), while accepting that local legislation and regulations will

continue to take precedence. The target audience includes regulators, logisticians and pharmaceutical professionals in industry, government and the international agencies.

The document has been prepared in close consultation with the WHO Task Force on Regulatory Oversight on Pharmaceutical Cold Chain Management which has been central to the review process. A full list of members is given at the end of this annex.

The intention is that the guidance in this document should be directly applicable in less-developed countries as well as in the industrialized world. To this end, supplementary materials will be developed to show how the requirements can practicably be achieved, particularly in resource-constrained settings. Experience with vaccine supply chain assessments in many less-developed countries demonstrates that the mandatory standards set out in this document can be achieved, and that some countries are also capable of meeting many of the optional requirements.

The document is designed to give a balanced overview of the major aspects of good storage and distribution practice for TTSPPs. As such it deliberately includes references to requirements which can be found in general guides to good manufacturing practice (GMP), good storage practice (GSP) and good distribution practice (GDP). The purpose is not to supplant these source materials, but to ensure that the reader is aware of the relevant GMP, GSP and GDP implications when seen from the particular and specialized perspective of TTSPPP management.

Key to conventions used

The following conventions are used in the requirements clauses:

- The imperative voice is used to denote a mandatory or highly desirable requirement. For example: “Ensure that...”, “Provide...” and the like.
- The words “where possible” or “preferably” are used to denote an optional but desirable requirement.
- Many clauses are followed by a brief explanation setting out the underlying reason for including the clause.

Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

active systems

Actively powered systems using electricity or other fuel source to maintain a temperature-controlled environment inside an insulated enclosure under thermostatic regulation (e.g. cold rooms, refrigerators, temperature-controlled trucks, refrigerated ocean and air containers).

change control

The processes and procedures to manage system changes.

common carrier

A seller of distribution services.

controlled or hazardous time- and temperature-sensitive pharmaceutical products

Time- and temperature-sensitive pharmaceutical products (TTSPPs) with high illicit value: poisons, narcotics, psychotropic products, inflammable or explosive substances and radioactive materials.

dunnage

Loose packing material used to protect TTSPPs from damage during transport.

external distribution

Transport of TTSPPs through various steps in the customer's supply chain (i.e. transport from a pharmaceutical manufacturer's distribution centre to commercial customers (including wholesalers, retailers and buying groups), to clinical facilities or direct to the patient).

installation qualification

The process of obtaining and documenting evidence that equipment has been provided and installed in accordance with its specifications and that it functions within predetermined limits when operated in accordance with the operating instructions.

internal distribution

Transport of a TTSPP within a pharmaceutical manufacturer's internal supply chain (i.e. all internal transports from manufacturing facility to packaging facility to warehouse to distribution centre).

net storage capacity

The total volume available for storing TTSPPs, taking account of the type of load support system employed (floor-standing pallets, adjustable pallet racking or shelving units), as modified by the utilization factor that can be achieved in the store.

passive systems

Systems which maintain a temperature-controlled environment inside an insulated enclosure, with or without thermostatic regulation, using a finite amount of pre-conditioned coolant in the form of chilled or frozen gel packs, phase change materials, dry ice or others.

pests

Includes birds, bats, rodents and insects whose uncontrolled presence affects hygiene and cleanliness.

pharmaceutical product

Any product intended for human use or veterinary product intended for administration to food-producing animals, presented in its finished dosage form, that is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required, products which may be sold to patients without a prescription, biologicals and vaccines. It does not, however, include medical devices.¹

qualification

Documented testing that demonstrates, with a high degree of assurance, that a specific process will meet its predetermined acceptance criteria.²

refrigeration equipment

The term “refrigeration” or “refrigeration equipment” means any equipment whose purpose is to lower air and product temperatures and/or to control relative humidity.

service level agreement (SLA)

A service level agreement or contract is a negotiated agreement between the customer and service provider that defines the common understanding about materials or service quality specifications, responsibilities, guarantees and communication mechanisms. It can either be legally binding, or an information agreement. The SLA may also specify the target and minimum level performance, operation or other service attributes.³

standard operating procedure (SOP)

A set of instructions having the force of a directive, covering those features of operations that lend themselves to a definite or standardized procedure without loss of effectiveness.

storage temperature

The temperature range listed on the TTSPP label, and within the regulatory documentation, for long-term storage.

storage unit temperature/humidity distribution

The range and pattern of temperatures and/or humidity within a temperature-controlled storage unit during normal operation.

¹ Definition from *Revision of WHO good distribution practices for pharmaceutical products*. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth report*. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 5.

² Definition from the Parenteral Drug Association (PDA) Technical Report No. 39, 2007.

³ Definition from International Air Transport Association (IATA), Chapter 17, 9th ed., June 2009.

suspect product

A TTSPP whose presentation and/or pharmacological formulation indicates that it has not been manufactured by the company named on the packaging. A TTSPP that shows visible or pharmacological evidence of tampering.

temperature-controlled

Includes any environment in which the temperature is actively or passively controlled at a level different from that of the surrounding environment within precise predefined limits.

temperature excursion

An excursion event in which a TTSPP is exposed to temperatures outside the range(s) prescribed for storage and/or transport. Temperature ranges for storage and transport may be the same or different; they are determined by the product manufacturer, based on stability data.

temperature-modified

Includes any environment in which the temperature is predictably maintained at a level different from that of the surrounding environment, but is not actively or passively controlled within precise predefined limits.

time- and temperature-sensitive pharmaceutical product (TTSPP)

Any pharmaceutical good or product which, when not stored or transported within predefined environmental conditions and/or within predefined time limits, is degraded to the extent that it no longer performs as originally intended.

transport temperature profile

Anticipated ambient temperature variation and duration to which a TTSPP may be exposed during transport.

utilization factor

The percentage of the total volume available for storing TTSPPs that can reliably be achieved in practice, taking account of the types of stock-keeping unit (SKU), the types of load support system and the stock management systems used in the store.

validation

Documented testing performed under highly controlled conditions, demonstrating that processes, methods, and systems consistently produce results meeting predetermined acceptance criteria.⁴

⁴ Definition from PDA Technical Report No. 39, 2007.

1. Importation

1.1 Port handling and customs clearance

1.1.1 Port of entry

Import TTSPPs through a port of entry that is equipped to handle such products. Where this is not possible, ensure that arrangements are in place to provide the necessary level of protection and security.

Reason: To minimize the risk of damage.

1.1.2 Offloading

As soon as possible after arrival, remove TTSPP shipments from the wharf or airport apron to a safe and suitable temperature-controlled storage location.

Reason: To minimize the risk of theft and to avoid exposure to adverse ambient conditions.

1.1.3 Temporary storage at port of entry

Store TTSPP shipments in a secure warehouse under the conditions recommended by the product manufacturer, until the shipment has been authorized for removal by customs.⁵

Reason: To avoid risk of theft or damage during temporary storage.

1.1.4 Customs clearance

Draw up procedures and memoranda of understanding to ensure that TTSPP shipments are cleared through customs as rapidly as possible. This can be facilitated by a pre-clearance procedure carried out by the local health agency, clearing agent or freight forwarder in collaboration with customs. Alternatively the clearance process should be conducted by customs staff, supported by personnel with suitable pharmaceutical training, especially when clearance involves the opening and resealing of temperature-controlled packaging.

Reason: To avoid delays during customs clearance that may cause temperature excursions and place TTSPPs at risk.

⁵ In some situations, arrangements can be made for formal customs clearance to take place away from the port of entry — for example, at a national vaccine store. In situations where the port of entry is not equipped with suitable cold storage facilities, this can reduce the risk of temperature excursions.

2. Warehousing sites

2.1 Site layout

2.1.1 Natural hazards

Select and/or develop storage sites to minimize risks from natural hazards such as floods, landslides and earthquakes and extreme weather conditions such as hurricanes and tornadoes.

Reason: To protect against loss of valuable pharmaceutical products, to ensure continued supply to patients in the market and to protect personnel working in the store.

2.1.2 Site access

Provide vehicular access to storage buildings sufficient to accommodate the largest vehicles visiting the site, including emergency vehicles.

Reason: To ensure convenient operation of the facility.

2.2 Site security

Provide perimeter protection to ensure security of the grounds and storage buildings against anticipated risks.

Reason: To protect against vandalism, theft and other illegal incursions. Security arrangements should be appropriate to the site location and the value of goods stored there.

2.3 Site cleanliness

Keep the site free of accumulated dust, dirt, waste and debris. Ensure that pests are kept under control within the site area. Collect waste in designated closed containers and arrange for safe disposal at frequent intervals.

Reason: To help protect storage buildings against ingress by dust, dirt and pests.

3. Storage buildings

3.1 Construction standards

Construct or procure storage buildings that are:

- purpose-designed for the storage of TTSPPs, or well-adapted for this purpose;
- designed to suit the prevailing climate, making maximum use of passive heating, cooling and ventilation;

- designed and equipped to minimize the consumption of electricity and other fuel sources;
- constructed using materials and finishes that are robust, easy to clean and which are selected to minimize long-term maintenance;
- constructed using locally available materials and building technologies; and
- built to minimize hiding and nesting places for pests.

Reasons: Storage in unsuitable and poorly-designed buildings places TTSPPs at risk and increases storage costs. Buildings constructed using inappropriate materials and technologies are difficult to operate and maintain in resource-constrained settings.

3.2 Accommodation and layout

Ensure that the storage buildings are well laid out and contain all the necessary storage areas, goods assembly, receiving and dispatch bays and office accommodation needed for efficient operation of the TTSP store.

3.3 Loading and receiving bays

3.3.1 Loading bays

Ensure that receiving and dispatch bays are designed to avoid conflict between incoming and outgoing goods and are protected from direct sunlight, dust, dirt, rain, snow and wind, and from extremes of heat, cold and solar radiation that could damage TTSPPs, and measures are taken to minimize pest activity in these areas.

Reason: Protection against damage and maintenance of product quality.

3.3.2 Receiving bays

Provide receiving areas with suitable equipment to clean reusable transport containers after their contents have been unloaded, and before the containers are stored for re-use.

Reason: Protection against contamination of outgoing TTSPPs.

3.4 Goods assembly and quarantine areas

3.4.1 Goods assembly areas

Provide sufficient space to receive, assemble and pack TTSPPs for dispatch under temperature-modified conditions. Preferably, these areas should be physically close to the temperature-controlled storage area.

Reason: Protection of TTSPPs during arrival, order assembly and dispatch.

3.4.2 Holding area for incoming goods

Provide a temperature-controlled holding area for incoming TTSPPs pending their acceptance into the main storage area. The holding area may be a physically separated zone, or it may be defined using a suitable stock control information system, or by a combination arrangement. Where goods are held in bond in the warehouse, awaiting customs clearance, they must be physically separated and secured.

Reason: Incoming items may need inspection and/or regulatory clearance, including laboratory testing.

3.4.3 Quarantine area

Provide a quarantine area for the isolation of returned, faulty, recalled and otherwise withdrawn goods pending a decision on disposal or re-stocking by the qualified person or department. Materials within quarantine areas must be clearly identified with their status.

- with temperature control, for items returned for re-stocking;
- with temperature control, for items recalled for testing;
- without temperature control, for items awaiting disposal.

The quarantine area may be a physically separated zone, or it may be defined using a suitable stock control information system, or by a combination arrangement.

Reason: Items for re-stocking, testing and disposal should be kept separate to avoid the risk of inappropriate use.

3.5 Environmental control of ancillary areas

Ensure, where possible, that ancillary areas where TTSPPs are temporarily held during arrival, order assembly or dispatch are:

- maintained within the temperature range specified for the goods being handled;
- maintained within the humidity range specified for goods that are adversely affected by high relative humidity and are not sufficiently protected by their packaging;⁶
- protected from undue exposure to direct sunlight;
- protected from the weather;
- protected against dust, dirt and waste accumulation;

⁶ Active environmental control of ancillary areas may not be needed if all TTSPPs are kept in temperature-controlled packaging and/or humidity-protective packaging when passing through these areas.

- adequately ventilated;
- adequately lit to enable operations to be carried out accurately and safely;
- monitored during the times when TTSPPs are handled; and monitored during the times when TTSPPs are handled (see 4.5.1-4.5.4).

Reason: Protection of TTSPPs quality during arrival, order assembly or dispatch.

3.6 Building security

3.6.1 General building security

Ensure that buildings used to store TTSPPs have sufficient security to prevent unauthorized access and to prevent misappropriation of goods.

Reason: To protect against vandalism, theft and other illegal incursions. Security arrangements should be appropriate to the site location and to the value of goods stored there.

3.6.2 Controlled and hazardous substances areas

Ensure that all areas that are used to store controlled or hazardous TTSPPs are:

- dedicated, securely locked facilities that comply fully with all legislative and regulatory requirements applicable in the country where the store is located;
- only accessible to authorized staff;
- protected by automatic intruder and/or fire and smoke, and/or chemical and/or radiological sensor alarm systems appropriate to the type(s) of product being stored;⁷
- designed to be explosion-proof, where explosive TTSPPs are stored;⁸ and
- continuously monitored by security staff.

Reason: Protection of property and life.

3.7 Fire protection

3.7.1 Fire protection equipment

Provide suitable fire detection and fire-fighting equipment, including fire hydrants, in all TTSPP storage areas and ensure that:

⁷ Zoned sprinkler systems are recommended to control fires and to localize product damage in the event of system activation.

⁸ Explosion-proof stores must have a blast roof or wall. Preferably, explosive substances should be stored in an independent building, well separated from the main store.

- systems and equipment are appropriate for the class of occupancy and product storage arrangements and are approved by the local fire authority; and
- equipment is regularly serviced in accordance with the equipment manufacturers' recommendations and local regulations.

Reason: Protection of property and life.

3.7.2 Fire prevention, detection and control procedures

Follow standard operating procedures (SOPs) for fire prevention, detection and control. Train staff and carry out regular fire drills. Prohibit smoking in all areas.

Reason: Protection of property and life.

3.8 Building hygiene

3.8.1 Building cleanliness

Implement a cleaning programme for all areas:

- do not allow the accumulation of dust, dirt and waste, including packaging waste;
- take precautions against spillage or breakage, and cross-contamination;
- collect waste in designated closed containers and arrange for safe disposal at frequent intervals;
- do not permit consumption of food or beverages other than in designated areas; and
- maintain cleaning records to demonstrate compliance.

Reason: Protection against damage and contamination of TTSPPs and to minimize the risk of pest infestation.

3.8.2 Pest control

Implement a programme to keep all areas free of pests. This should include enclosed receiving and loading bays. Maintain records to demonstrate compliance with a robust pest control programme.

Reason: Protection against damage and contamination of TTSPPs.

3.9 Power supply

3.9.1 Uninterrupted power supply

Where possible, and where necessary,⁹ ensure that all temperature-controlling equipment for TTSPPs storage (i.e. refrigerators, freezers, building management systems, heating, ventilation and air-conditioning (HVAC) systems, compressors, air-handling units, monitoring systems, alarms and related computer equipment) are connected to an uninterrupted power supply (UPS) system. Where a generator and associated control equipment is used it should:

- be able to manage the combined start-up load of all connected temperature-controlling and temperature-monitoring equipment;¹⁰
- not exceed the defined parameters of the mains power supply;
- be equipped with automatic mains failure start-up and automatic shutdown when power is restored; and
- have adequate fuel tank capacity and sufficient fuel to cover a prolonged power outage.

Regularly test and service UPS equipment and generators. Maintain records to demonstrate compliance.

Reason: Loss prevention.

3.9.2 Power failure contingency plan

Develop and maintain a contingency plan to protect TTSPPs in the event of power failure which places products at risk. Alternative emergency cooling systems (e.g. liquid nitrogen or dry ice) are acceptable.

Reason: Loss prevention.

3.10 Building maintenance

Implement a planned preventive maintenance programme to ensure that storage buildings and building utilities are well maintained. Keep records to demonstrate compliance with the programme.

Reason: To ensure that storage buildings continue to protect stored products against damage.

⁹ UPS systems may be unnecessary in countries with a very reliable electricity supply. In smaller stores in countries where electricity is only available for a limited period each day, or is entirely absent, an alternative approach to UPS is to use refrigeration equipment with extended holdover capacity, for example, ice-lined refrigerators, or gas, kerosene or solar-powered refrigerators.

¹⁰ The installed capacity of the UPS system can be minimized by fitting electronic controls which reduce compressor start-up loads.

4. Temperature-controlled storage

4.1 Normative references

- EN 60068-3 parts 5, 6, 7 and 11: *Environmental testing. Guidance. Confirmation of the performance of temperature chambers*
- International Air Transport Association (IATA) *Perishable cargo regulations chapter 17.* 10th ed, July 2010
- USP <1079> *Good storage and shipping practices*
- USP <1118> *Monitoring devices — time, temperature and humidity*

4.2 Storage capacity of temperature-controlled stores

Ensure that the net storage capacity of the temperature-controlled stores is sufficient to accommodate peak TTSPP stock levels and their associated transit temperature protection components (i.e. freezer blocks, flexible ice blankets, refrigerated gel packs, phase change materials and insulated packaging, if retained), under correct temperature conditions and in a manner which enables efficient and correct stock management operations to take place.

Reason: To avoid the risks associated with overstocking and to ensure that good warehousing practices can be adopted (i.e. first in-first out (FIFO) or earliest expiry-first out (EEFO)). Overstocking makes FIFO or EEFO handling difficult or impossible and hinders accurate physical stock counts.

4.3 Temperature-controlled storage

Ensure that TTSPPs are stored in temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers which comply with the following requirements.

Temperature-controlled rooms, cold rooms and freezer rooms should be:

- capable of maintaining the temperature range defined by the system set points over the full annual ambient temperature range experienced at the store location;
- preferably equipped with an auto-defrost circuit which has a minimal effect on temperature within the unit during the defrost cycle and maintains temperature within specification for this period;
- equipped with a low temperature protection circuit in cold climates where there is a risk of breaching the low temperature set point for TTSPPs that are damaged by exposure to low temperatures;
- connected to a UPS as described in clause 3.9.1;

- equipped with a calibrated continuous temperature monitoring system with sensors located at points representing greatest temperature variability and temperature extremes;
- preferably equipped with continuous humidity monitoring devices with sensors located at points representing humidity extremes;
- equipped with alarms to indicate temperature excursions and/or refrigeration failure;
- fitted with lockable doors, or an access control system, as necessary; locks must have a safety device so that doors can be freely opened from the inside; and
- qualified as defined in clause 4.7.

Refrigerators and freezers should be:

- purpose-designed for the storage of TTSPPs; household-style units are only acceptable if they have been independently tested and found to comply with the temperature control requirements of a recognized standard for pharmaceutical refrigerators and freezers;
- capable of maintaining the temperature range specified by the TTSPP manufacturer over the full annual ambient temperature range experienced at the storage site;
- equipped with calibrated temperature monitoring devices appropriate to the level of risk but preferably capable of continuous recording and with sensor(s) located at a point or points within the cabinet which most accurately represents the temperature profile of the equipment during normal operation;
- preferably equipped with alarms to indicate temperature excursions and/or refrigeration failure;
- fitted with lockable doors or lids, or access control system, as necessary; and
- qualified and/or tested as defined in clause 4.7.

Reason: To maintain labelled TTSPP storage temperatures during long-term storage.

4.4 Temperature-controlled storage for controlled and hazardous products

Ensure that controlled and hazardous TTSPPs are securely stored:

- Provide dedicated temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers for these TTSPPs, in separate secure areas, as described in clause 3.6.2.
- Alternatively, but only if acceptable to the regulatory authority, bulk stocks of TTSPPs with high illicit-value may be stored in a securely locked section of a general temperature-controlled storage area.

Reason: To protect this category of TTSPPs against theft and misuse and to safeguard workers and general storage areas in the event of an accident involving hazardous substances.

4.5 Temperature and humidity control and monitoring in storage

4.5.1 Temperature control

Provide thermostatic temperature control systems for all temperature- controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPPs. Comply with the following minimum requirements:

- system able continuously to maintain air temperatures within the set point limits throughout the validated storage volume;
- control sensors accurate to $\pm 0.5^{\circ}\text{C}$ or better;
- control sensors calibrated as described in clause 4.10.1;
- control sensors located in areas where greatest variability in temperature is expected to occur in order to maximize available safe storage volume;
- control sensors positioned at the hot and cold spots determined by temperature mapping, even if affected by door opening, unless recommendations are being made not to store products in such areas; and
- control sensors independent of the temperature monitoring system.

4.5.2 Temperature monitoring

Provide air temperature monitoring systems and devices for all temperature- controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPPs. Comply with the following minimum requirements:

General requirements

- Monitoring sensors accurate to ± 0.5 °C or better for electronic devices and ± 1 °C or better for alcohol, bi-metal gas or vapour pressure thermometers.
- Monitoring sensors calibrated as described in clause 4.10.1.
- Monitoring sensors located in areas where greatest variability in temperature is expected to occur within the qualified and/or tested storage volume as defined in clause 4.7.
- Monitoring sensors positioned so as to be minimally affected by transient events such as door opening.
- Temperature monitoring devices, temperature traces or electronic temperature records manually checked at least twice a day, in the morning and evening, seven days a week, including public holidays.

Temperature-controlled rooms, cold rooms and freezer rooms

- Provide a temperature record with a minimum recording frequency of six times per hour for each monitoring sensor position.
- Provide documentation for each monitoring sensor position which can be stored and accessed.
- Continue to operate independently in the event of a power failure.¹¹

Refrigerators and freezers

- Preferably, connect refrigerators and freezers to a multipoint monitoring system with a minimum recording frequency of six times per hour for each sensor position which can operate independently in the event of a power failure.
- Alternatively use battery-powered portable temperature monitoring devices with a minimum recording frequency of six times per hour.
- The least preferred option is a thermometer or maximum/minimum thermometer.
- Provide documentation for each appliance which can be stored and accessed.

¹¹ Where there is no UPS, the autonomy period for the device should be matched to the maximum length of anticipated power outages.

Reasons: To maintain labelled TTSPP temperatures during long-term storage. Thermometers provide only limited and discontinuous temperature information. For this reason, continuous recording devices are preferable.

4.5.3 Humidity control

Provide humidity control in temperature-controlled rooms that are used to store TTSPPs which are adversely affected by high relative humidity and are not sufficiently protected by their packaging. Such products are typically labelled “store in a dry place”, or carry similar wording and require a humidity-controlled environment.

4.5.4 Humidity monitoring

Provide humidity monitoring systems and devices in temperature-controlled rooms that are used to store TTSPPs which require a humidity-controlled environment. Comply with the following minimum requirements:

- sensors accurate to $\pm 5\%$ RH;
- sensors calibrated as per clause 4.10.2;
- sensors located to monitor worst-case humidity levels within the qualified storage volume defined in clause 4.7;
- sensors positioned so as to be minimally affected by transient events such as door opening;
- provides a humidity record with a minimum recording frequency of six times per hour for each sensor position;
- provides documentation for each sensor position which can be stored and accessed; and
- continues to operate independently in the event of a power failure.¹²

Reason: To maintain labelled TTSPP humidity conditions during long-term storage.

4.6 Alarm systems

4.6.1 Temperature alarms

Provide temperature alarm systems for temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, used to store TTSPPs. Comply with the following minimum requirements:

¹² Where there is no UPS the autonomy period for the device should be matched to the maximum length of anticipated power outages.

General requirements

- Sensors accurate to ± 0.5 °C.
- Sensors calibrated as described in clause 4.10.1.
- Sensors located to monitor worst-case temperatures within the validated storage volume defined in clause 4.7; where the alarm system is not integrated with the temperature monitoring system, sensors should be located close to the temperature monitoring sensors.
- Sensors positioned so as to be minimally affected by transient events such as door opening.

Temperature-controlled rooms, cold rooms and freezer rooms

- High/low alarms set points to trigger appropriately located visual alarm(s).
- Preferably there should also be appropriately located audible alarm(s) in addition to the visual alarm(s).
- Preferably there should be an automatic telephone dial-up or SMS text warning system to alert on-call personnel when an alarm is triggered outside working hours.

Refrigerators and freezers

- Preferably there should be a visual and/or audible alarm system; this may be integrated with a portable continuous temperature monitoring device.

Reason: Loss prevention.

4.6.2 Humidity alarms

Provide humidity alarm systems for temperature-controlled rooms used to store TTSPPs that require a humidity-controlled environment. Comply with the following minimum requirements:

- sensors accurate to $\pm 5\%$ relative humidity (RH);
- sensors calibrated as described in clause 4.10.2;
- sensors located to monitor worst-case humidity levels within the validated storage volume defined in clause 4.7; where the alarm system is not integrated with the humidity monitoring system, sensors should be located close to the humidity monitoring sensors;
- sensors positioned so as to be minimally affected by transient events such as door opening;

- high/low alarms set points to trigger appropriately located visual alarm(s);
- preferably there should also be appropriately located audible alarm(s) in addition to the visual alarm(s); and
- preferably there should be an automatic telephone dial-up or SMS text warning system to alert on-call personnel when an alarm is triggered outside working hours.

Reason: Loss prevention.

4.7 Qualification of temperature-controlled stores

Qualify new temperature-controlled storage areas and new refrigeration equipment before it becomes operational. The qualification procedure should:

- demonstrate the air temperature profile throughout the storage area or equipment cabinet, when empty and in a normal loaded condition;
- define zones which should not be used for storage of TTSPPs (for example areas in close proximity to cooling coils, cold air streams or heat sources); and
- demonstrate the time taken for temperatures to exceed the designated limits in the event of power failure.

Fully document the initial qualification. Carry out additional qualification exercises whenever modifications are made to the storage area that may increase loading or affect air circulation, or when changes are made to the refrigeration equipment, such as a change in the set point. Consider the need for requalification whenever temperature and/or humidity monitoring shows unexplained variability that is greater than normal.

Qualification may not be required for equipment which requires little or no site assembly or commissioning, such as vaccine refrigerators and freezers that have been independently tested and found suitable for the storage of TTSPPs. Independent testing must be carried out between the chosen set points and under the ambient temperature conditions to which the equipment will be exposed during operation. Prequalified equipment of this type must be correctly installed in each location in accordance with written guidance.

Reason: To ensure that labelled TTSPPs temperatures can be maintained during long-term storage and that the facility can demonstrate to the regulatory authorities and other interested parties that due diligence has been observed.

4.8 Cleanliness of temperature-controlled stores

Implement a cleaning and decontamination programme for all temperature-controlled rooms:

- Ensure that floor areas are fully accessible for cleaning. Do not store goods directly on the floor.
- Do not permit storage of any non-pharmaceutical products except transport-related items such as icepacks, gel packs and the like.
- Do not allow the accumulation of dust, dirt and waste, including packaging waste.
- Take precautions against spillage or breakage, and cross-contamination.
- Do not allow accumulation of frost and ice, particularly ice contaminated by spillages.
- Collect waste in designated closed containers and arrange for safe disposal at frequent intervals.

Maintain cleaning records to demonstrate compliance.

Reason: Protection against damage and contamination of TTSPPs and hazards to workers, arising from spillage or breakage.

4.9 Refrigeration equipment maintenance

Implement a maintenance programme for all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers:

- Carry out regular planned preventive maintenance on all temperature-controlling equipment.
- Make arrangements to ensure that emergency maintenance is carried out within a time period that does not place TTSPPs at risk of damage.
- Ensure that there is a contingency plan to move products stored in non-functioning equipment to a safe location before damage to the product occurs in the event that equipment cannot be repaired in a timely manner.

Maintain records to demonstrate compliance.

Reason: Loss prevention.

4.10 Calibration and verification of control and monitoring devices

4.10.1 Calibration of temperature control and monitoring devices

Calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified. Calibration should demonstrate the accuracy of the unit across the entire temperature range over which the device is designed to be used. Single-use devices that are supplied with a manufacturer's calibration certificate do not need to be re-calibrated.

4.10.2 Calibration of humidity control and monitoring devices

Calibrate devices against a certified, traceable reference standard at least once a year unless otherwise justified. Single-use devices that are supplied with a manufacturer's calibration certificate do not need to be re-calibrated.

4.10.3 Alarm equipment verification

Check functionality of temperature and humidity alarms at least once every six months at the designated set points.

Maintain records to demonstrate compliance.

Reason: To ensure that labelled TTSPP storage temperatures and humidity control can be maintained during long-term storage and that the store can demonstrate to the regulatory authorities and other interested parties that due diligence has been observed.

5. Materials handling

5.1 Materials handling equipment

Where powered materials handling equipment is used in temperature- controlled rooms, cold rooms or freezer rooms, select equipment which is certified for safe use in confined spaces.

Reason: Protection of the workforce.

6. Transport and delivery

6.1 Normative references

- Directive 94/62/EC. *European Parliament and Council Directive of 20 December 1994 on packaging and packaging waste.* 1994.
- EN 13428:2004. *Packaging. Requirements specific to manufacturing and composition. Prevention by source reduction.*
- EN 13430:2004. *Packaging. Requirements for packaging recoverable by material recycling.*
- EN 13431:2004. *Packaging. Requirements for packaging recoverable in the form of energy recovery, including specification of minimum inferior calorific value.*
- EN 13432:2000. *Packaging. Requirements for packaging recoverable through composting and biodegradation. Test scheme and evaluation criteria for the final acceptance of packaging.*

- IATA *Perishable Cargo Regulations Chapter 17*, 9th Edition, July 2009.
- *Isothermal and refrigerating containers for health products — Thermal performance qualification method.*
- ISTA — 5B: *Focused Simulation Guide for Thermal Performance Testing of Temperature Controlled Transport Packaging.*
- ISTA — 7D: *Thermal Controlled Transport Packaging for Parcel Delivery System Shipment. Basic Requirements: atmospheric conditioning, vibration and shock testing.*
- WHO Technical Report Series, No. 937, 2006. Annex 5: *Good distribution practices for pharmaceutical products.*

6.2 Product stability profiles

Transport TTSPPs in such a manner that transport temperatures meet local regulatory requirements at the sending and receiving sites and/or so that temperature excursions above or below the manufacturer's labelled storage temperature range do not adversely affect product quality. Product stability data must demonstrate the acceptable temperature excursion time during transport.

Reason: Protection of TTSPPs against degradation.

6.3 Transport route profiling and qualification

Profile and qualify transport routes:

- Select the most suitable methods for protecting TTSPPs against anticipated ambient temperature and humidity conditions throughout the year.
- Use suitable methods, including published standards, weather data, laboratory tests and field tests to select suitable transport equipment and shipping containers.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.4 Temperature-controlled transport

6.4.1 Air and sea transport

Ensure that any carrier contracted to transport TTSPPs by air or by sea operates under the terms of a formal service level agreement (SLA) drawn up between the parties. The carrier is to be made responsible for maintaining load temperatures within the transport temperature profile defined for each product.

Reason: To ensure that the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product and that compliance can be demonstrated to the contracting organization, the regulatory authorities and other interested parties.

6.4.2 Temperature-controlled road vehicles operated by common carriers

Temperature control in vehicles operated by a common carrier must be qualified and the details and responsibilities for this process should be set out in a formal SLA drawn up between the parties.

Reason: To ensure that the carrier is made responsible for maintaining load temperatures within the transport temperature profile defined for each product and that compliance can be demonstrated to the contracting organization, the regulatory authorities and other interested parties.

6.4.3 Temperature-controlled road vehicles generally

Ensure that temperature-controlled road vehicles used for the transport of TTSPPs are:

- capable of maintaining the temperature range defined by the system set points over the full annual ambient temperature range experienced over known distribution routes and when the vehicle is in motion, or parked with the main engine stopped;
- equipped with a low temperature protection circuit in cold climates where there is a risk of breaching the low temperature set point for TTSPPs that are damaged by exposure to low temperatures;
- equipped with calibrated temperature monitoring devices with sensors located at points representing temperature extremes;
- equipped with alarms to alert the driver in the event of temperature excursions and/or refrigeration unit failure;
- fitted with doors with security seals and/or security locks that protect against unauthorized access during transit;
- qualified as defined in clause 6.6; and
- regularly calibrated and maintained and records kept to demonstrate compliance.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.4.4 Transport of controlled TTSPPs and TTSPPs with high illicit value

Ensure that controlled TTSPPs and TTSPPs with high illicit value are transported in the following manner:

- Transport practices comply with all relevant local legislation and regulations.
- Vehicles are equipped with lockable doors and an intruder alarm.
- Vehicles use unique seal lock indicating devices such as cable seal locks with unique identifiers that are tamper-resistant to protect against unauthorized access during transit.¹³
- Security-cleared delivery drivers are employed.
- All deliveries are documented and tracked.
- Signed dispatch and arrival records are kept.
- Shipments are fitted with security equipment appropriate to the product being transported and the assessed security risk, such as global positioning system (GPS) devices located in the vehicle and/or hidden in the product.
- Drivers are informed about the perishability of the product and the maximum acceptable transport time.

Reason: To prevent theft and misappropriation of this category of TTSPP and to ensure the security and safety of the driver.

6.5 Temperature and humidity control and monitoring during transit

6.5.1 Temperature control in temperature-controlled road vehicles

Provide thermostatic temperature control systems for all temperature-controlled vehicles used to transport TTSPPs. Comply with the following minimum requirements:

- system able continuously to maintain air temperatures within the set point limits throughout the validated storage volume defined in clause 6.6;
- control sensors accurate to $\pm 0.5^{\circ}\text{C}$;
- control sensors calibrated as described in clause 6.7.1;
- control sensors located to control worst-case temperatures in order to maximize available safe storage volume;
- control sensors positioned in the return air stream; and
- control sensors independent of the temperature monitoring system.

¹³ Refer to ISO/PAS 17712: *Freight containers — Mechanical seals*.

6.5.2 Temperature monitoring in temperature-controlled road vehicles

Provide air temperature monitoring systems and devices for vehicles used to transport TTSPPs. Comply with the following minimum requirements:

- monitoring sensors accurate to $\pm 0.5^{\circ}\text{C}$;
- monitoring sensors calibrated as described in clause 6.7.2;
- monitoring sensors located to monitor worst-case temperatures within the qualified storage zone defined in clause 6.6;
- monitoring sensors positioned so as to monitor worst-case positions;
- provide a temperature record with a minimum recording frequency of six times per hour for each sensor position;¹⁴ and
- provide documentation which can be stored and accessed.

Establish transit temperature specifications and document transit temperatures for every internal and external shipment.

6.5.3 Humidity monitoring in temperature-controlled road vehicles

Preferably provide humidity monitoring systems and devices for temperature-controlled vehicles which are used to transport TTSPPs that require a humidity-controlled environment. Systems and devices should comply with the following minimum requirements:

- sensors accurate to $\pm 5\%$ RH;
- sensors calibrated as described in clause 6.7.3;
- sensors located to monitor worst-case humidity levels within the qualified storage zone defined in clause 6.6;
- sensors positioned so as to be minimally affected by transient events such as door opening;
- provide a humidity record with a minimum recording frequency of six times per hour for each sensor position; and
- provide documentation which can be stored and accessed.

Establish transit humidity specifications and document transit humidity conditions for internal and external shipments where required.

¹⁴ Recording frequency should take account of the storage capacity of the data logger and the expected transport period.

6.5.4 Temperature monitoring in passive and active shipping containers

Use chemical or electronic freeze indicators, electronic loggers (with or without alarms) and/or other suitable indicators to monitor temperature and/or humidity exposure during internal distribution. Preferably use these devices for external distribution. Monitor and document indicator status upon arrival.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.6 Qualification of temperature-controlled road vehicles

Where temperature-controlled vehicles are directly owned and/or operated, qualify each vehicle before it becomes operational, wherever possible. The qualification procedure should:

- demonstrate that the air temperature distribution is maintained within the limits specified throughout the temperature-controlled compartment for both air and product temperatures for commonly used load layouts and at the ambient temperature extremes anticipated during normal operation over known routes;
- demonstrate the humidity distribution throughout the temperature-controlled compartment for commonly used load layouts, where products are being transported that require a humidity-controlled environment;
- define zones within the vehicle's payload area which should not be packed with TTSPPs (for example areas in close proximity to cooling coils or cold air streams);
- demonstrate the time taken for temperatures to exceed the designated maximum in the event that the temperature-controlling unit fails; and
- document the qualification exercise.

An alternative approach is to perform an initial full qualification on each trailer/refrigeration unit type combined with an installation qualification (IQ) for each example when a new vehicle becomes operational.

Carry out additional qualification exercises whenever significant modifications are made to the vehicle. Consider the need for requalification whenever temperature and/or humidity monitoring shows unexplained variability that is greater than normal.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.7 Calibration and verification of transport monitoring devices

6.7.1 Calibration of transport temperature control devices

Calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified.

6.7.2 Calibration of transport temperature monitoring devices

Calibrate devices against a certified, traceable reference standard at least once a year, unless otherwise justified.

6.7.3 Calibration of transport humidity monitoring devices

Calibrate devices against a certified, traceable, reference standard at least once a year, unless otherwise justified.

6.7.4 Verification of transport alarm equipment

Check functionality of temperature and humidity alarms at the designated set points. Check functionality of security alarm systems. Carry out these checks at least once a year, unless otherwise justified.

Maintain records to demonstrate compliance.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.8 Shipping containers

6.8.1 Container selection generally

Select shipping containers that:

- comply with applicable national and international standards relevant to the product type and the chosen transport route and mode(s);
- protect personnel and the general public from hazards arising from spillage, leakage or excessive internal pressure;
- protect the product being transported against mechanical damage and the anticipated ambient temperature range that will be encountered in transit; and
- can be closed in a manner that allows the recipient of the consignment to establish that the product has not been tampered with during transport.

Reason: Quality assurance and safety.

6.8.2 Uninsulated containers

Ensure that uninsulated containers are correctly used, in a manner which protects their contents:

- transport uninsulated containers in a qualified temperature-controlled environment such as an actively or passively temperature-controlled vehicle;
- ensure that the transport system is able to maintain the temperature of the TTSPP within the product's stability profile as stated by the product manufacturer and/or to maintain the TTSPP within the transit temperature specification requirements specified by the regulatory authorities at both the sending and receiving locations.

Reason: Quality assurance and safety.

6.8.3 Qualification of insulated passive containers

Qualify insulated passive containers, including any and all necessary ancillary packaging such as temperature stabilizing medium, dry ice, ice or gel packs, cool water packs or warm packs, phase change materials, partitions, bubble wrap and dunnage:

- ensure that the qualified packaging system is capable of maintaining the TTSPP within the temperature range needed to meet the product stability profile as stated by the product manufacturer. Container qualification should include full details of the packaging assembly, the thermal conditioning regime and the minimum and maximum shipping volume, weight and thermal mass that can safely be accommodated in the container. Qualification should also include the correct placement of temperature monitors where these are used;
- take account of the transport route and of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of arrival in the recipient's temperature-controlled store.

Reason: To ensure that TTSPPs can safely be transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.8.4 Qualification of active containers

Qualify active containers:

- ensure that the container is capable of maintaining the TTSPP within the temperature range needed to meet the product stability profile as stated by the product manufacturer;

- take account of the transport route and of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of arrival in the recipient's temperature-controlled store.

Reason: To ensure that TTSPPs can be safely transported within the transport temperature profile defined for each product and that compliance can be demonstrated to the regulatory authorities and other interested parties.

6.9 Shipping container packing

Pack TTSPPs shipping containers to:

- the exact specified configuration to ensure that the correct TTSPP temperature range is maintained;
- minimize the risk of theft and fraud and assure the recipient that the goods have not been tampered with while in transit, for example by using locked containers or shrink-wrapped pallets;
- minimize the risk of mechanical damage during transport;
- protect freeze-sensitive products against temperatures below 0 °C when frozen packs are used;
- protect products against light, moisture and contamination or attack by microorganisms and pests;
- protect products against adverse effects when dry ice is used as a coolant;
- clearly label containers to identify the correct transport temperature range and to show correct orientation for handling; and
- ensure that packages containing dangerous goods (including dry ice) are labelled in compliance with relevant transport regulations and requirements.

Reason: To ensure that shipping containers are systematically used in the manner defined during the container qualification process and that this can be demonstrated to the regulatory authorities and other interested parties.

6.10 Product handling during packing and transport

Handle TTSPPs correctly during packing and transport:

- pack TTSPPs in an area set aside for the assembly and packaging of these products as specified in clause 3.3.1;
- take precautions against spillage or breakage, contamination and cross-contamination;

- deliver TTSPPs to outside recipients by the most suitable mode(s) of transport available in order to minimize delivery time; and
- ensure that patients receiving TTSPP deliveries are given clear advice on correct storage of the product before use.

Reason: To maintain TTSPP quality during transport.

6.11 Cleaning road vehicles and transport containers

Implement a cleaning and decontamination programme for all road vehicles and reusable shipping containers used to transport TTSPPs:

- ensure that all internal surfaces of load compartments are regularly cleaned;
- do not allow the accumulation of dust, dirt and waste, including packaging waste in load compartments, or in reusable shipping containers;
- take precautions against spillage or breakage, and cross-contamination;
- do not allow accumulation of frost and ice in refrigerated vehicles, particularly ice contaminated by spillages; and
- collect waste in designated closed containers and arrange for safe disposal at frequent intervals.

Maintain cleaning records for vehicles and reusable shipping containers to demonstrate compliance.

Reason: Protection against damage and contamination of TTSPPs and hazards to workers arising from spillage or breakage.

6.12 Transport of returned and recalled TTSPPs

6.12.1 Transport of returned TTSPPs

Ensure that that returned TTSPPs are transported under the same conditions as those used for the initial delivery:

- the sender and recipient must work together so that that the product is maintained within the temperature range needed to meet the manufacturer's stated product stability profile;
- take account of the anticipated ambient temperature profile over the duration of transport, measured from the point of departure to the point of return; and
- quarantine returned TTSPPs in temperature-controlled storage pending a decision by the quality control department or qualified person to dispose of the product or to return it to stock.

Reason: To ensure that returned and recalled TTSPPs are maintained within the correct transport temperature profile so that they can safely be re-stocked if a decision to do so is made.

6.12.2 Transport of recalled TTSPPs

Ensure that recalled TTSPPs are:

- marked for disposal as either “recalled” or “withdrawn”;
- transported back from the recipient and quarantined under secure conditions pending a final decision on disposal as described in clause 8.6.3.

7. Labelling

7.1 Normative references

- *IATA Perishable Cargo Regulations Chapter 179th Edition, July 2009. Clauses 17.10.5 and 17.10.6.*

7.2 Labelling

7.2.1 Labelling generally

Label internal shipping and external distribution containers containing TTSPPs as follows:

- identify the product in accordance with all national and international labelling requirements relevant to the container content, transport route and mode(s);
- identify hazardous products in accordance with relevant national and international labelling conventions; and
- indicate the appropriate temperature and humidity ranges within which the product is to be transported and/or stored.

7.2.2 Labelling air-freighted shipments

In cases where TTSPPs are to be air-freighted, the package(s) should be labelled using the standard International Air Transport Association (IATA) time and temperature-sensitive symbol, in accordance with the conditions outlined in Chapter 17 of the IATA Perishable Cargo Regulations. Apply the label to the outer surface of individual shipping packages, overpacks or bulk containers.

Reason: To ensure that products are correctly and safely handled at all points in the supply chain.

8. Stock management

8.1 Stock control systems

8.1.1 General stock control systems and procedures

TTSPP stock control systems and procedures meet the following minimum requirements:

- allow access only to authorized persons;
- record all receipts and dispatches;
- record batch numbers and expiry dates;
- record short-dated and expired products;
- record product status (i.e. released, quarantined, hold, reject);
- record all product returns, recalls, withdrawals, damage and disposals;
- manage the issue of products in EEFO order; and
- take regular physical inventories and reconcile stock records with the actual physical count. Investigate and report on stock discrepancies in accordance with agreed procedures. Preferably physical counts should be made at least twice a year.

Reason: To ensure that accurate and complete stock records are kept at all times.

8.1.2 Stock control procedures for controlled and hazardous TTSPPs

In addition to the requirements set out in clause 8.1.1, implement the following procedures:

- Institute a customer verification process to ensure that all recipients of these products are authorized to receive them.
- Maintain stock records which specifically identify products in these categories.
- Carry out regular audits and make audit reports available to the responsible authorities.
- Comply with all record-keeping procedures specified in local legislation and regulations. Retain product transaction and delivery records for at least the minimum time period required by local regulations.

Reason: To ensure that accurate and complete stock records are kept at all times and to satisfy the requirements of the regulatory authorities.

8.2 Incoming goods

8.2.1 Product arrival checks

Check and record the following for all incoming TTSPPs:

- product name, item code (identifier), strength, and batch/lot number;
- quantity received against order;
- name and address of the supplying site;
- examine containers for tampering, damage or contamination;
- examine expiry dates — accept short-dated products only if prior agreement has been reached with the supplier; do not accept products that have expired or which are so close to their expiry date that this date is likely to occur before use by the consumer;
- delays encountered during transport;
- status of any attached temperature recording device(s) and/or time/temperature indicators; and
- verify that required storage and transport conditions have been maintained.

8.2.2 Actions following arrival checks

- Enter product details, including product name/number, strength, batch numbers, quantities received, expiry dates and acceptance status into the stock recording system.
- Store checked goods under the correct temperature and security regime immediately upon receipt.
- Quarantine defective or potentially defective products, products with incomplete or missing paperwork, products that experienced unacceptable temperature excursions during transport, or products suspected to be counterfeit. Do not release until checks have been completed satisfactorily. All unacceptable temperature excursions should be evaluated to determine their effect on the product.
- Report any defects to the supplying store or holder of the marketing authorization.
- Do not transfer to saleable stock until all relevant disposition procedures have been completed.

Reason: To ensure that incoming TTSPPs are in acceptable condition, accurately recorded and correctly stored and that defective and/or incorrect shipments are followed up with the supplier.

8.3 Outgoing goods (external deliveries)

8.3.1 Management of outgoing goods

Implement outgoing goods procedures to ensure that:

- Transport vehicle conformity, including conformity with SLA or quality assurance (QA) agreements, is checked before loading goods.
- Expired products are never issued.
- Products with short expiry dates are not issued unless the recipient accepts that they can be consumed before the expiry date is reached.
- Products are distributed in strict EEFO order unless a product-based time-temperature exposure indicator, such as a vaccine vial monitor, demonstrates that a batch should be distributed ahead of its EEFO order.
- Details of any temperature monitoring devices packed with the external distributions are recorded.
- Details of outgoing products, including product name/number, strength, batch numbers, expiry dates and quantities distributed, are entered into the stock recording system.

8.3.2 Actions following dispatch

Monitor TTSPPs following dispatch in order to:

- trace products to their intended destination;
- record and retain records to provide assurance of goods arrival status. A suitable delivery report from the carrier is an acceptable alternative; and
- take appropriate action in the event of returns, recalls or complaints.

Reason: To ensure that outgoing TTSPPs are in acceptable condition, that short-dated stock does not accumulate in the store and that evidence is kept to demonstrate that correct quantities are distributed and received in good condition.

8.4 Product complaint procedures

Manage product complaints as follows:

- If a product defect is discovered or suspected in a batch of TTSPPs, cooperate with the regulatory authority to determine whether other batches are affected and recall products if required to do so by the regulatory authority.
- Where complaints or defects relate to a product or its packaging, immediately notify the holder of the marketing authorization for the product.

- Where complaints or defects arise as a result of errors or omissions within the organization, immediately evaluate the causes and take remedial measures to prevent a recurrence.
- Record all complaints and the remedial actions taken. Monitor and analyse trends in the complaint records.

Reason: Protection of the public and of the reputation of the supplying organization.

8.5 Suspect product procedures

8.5.1 Suspect products

Implement systems for identifying and managing suspect products found in the supply chain as follows:

- Physically segregate any suspect TTSPPs found in the supply chain and store securely until legal investigations are complete.
- Label them clearly as “Not for use” or other similar phrase;
- Immediately notify the regulatory authority or authorities and any other relevant authorities, as well as the holder of the marketing authorization of the product.
- Cooperate with regulatory authorities to assist with investigating the source of suspect products and implement appropriate remedial action(s).
- Document the decision-making process for disposal or return of condemned or defective TTSPPs and make these records available to the relevant authorities.

Reason: Protection of the public, protection of legitimate suppliers and manufacturers and conformity with regulatory requirements.

8.6 Product return, recall, withdrawal and disposal procedures

8.6.1 Return procedures

Manage product returns as follows:

- Quarantine returned TTSPPs in a suitable temperature-controlled area and under the security conditions applicable to the product type.
- Do not return to saleable stock unless storage and transport temperature conditions after dispatch from the distribution site have been fully verified and documented, including the return leg to the distribution site.
- Where appropriate, obtain written advice from the holder of the marketing authorization regarding handling and/or disposal of the returned TTSPP.

- If returned stock is re-issued, distribute in EEFO order or in accordance with the exposure status of any product-mounted time-temperature indicator device.
- Quarantine returned TTSPPs that have been exposed to unacceptable storage and/or transport temperatures and mark for disposal.
- Maintain records of all returned TTSPPs.

Reason: Protection of the public.

8.6.2 Recall procedures

Manage product recalls as follows:

- Conduct urgent and non-urgent TTSPP recalls in accordance with an agreed emergency plan.
- Notify the local regulatory authority or authorities.
- Notify overseas regulatory counterparts where the product has been exported.
- Notify all affected customers as applicable.
- Quarantine any remaining inventory of recalled TTSPPs and mark for further investigation before disposal.
- Maintain records of all TTSPP recalls, including reconciliation of quantity sold, quantity returned, quantity remaining or quantity consumed.

Reason: Protection of the public and conformity with regulatory requirements.

8.6.3 Disposal procedures

Manage product awaiting board of survey or disposal as follows:

- Ensure that rejected and/or recalled or withdrawn TTSPPs cannot be used, released or cause contamination to other products. Store separately from other products, in accordance with local regulations, to await destruction or return to the supplier.
- Safely dispose of rejected and/or recalled/withdrawn products in accordance with local regulations, including where relevant, regulations covering the disposal of hazardous and controlled drugs.
- Maintain disposal records.

Reason: Protection of the public and the environment.

8.7 Traceability or stock tracking

Ensure that stock and distribution records enable traceability, or stock tracking, of TTSPPs from the point of supply to the end-user or patient.

Traceability should include records of the temperature exposure of the product during internal shipping and storage. These records should include:

- for incoming goods: status of shipping indicators used (if any), status of product-based time-temperature indicators (if any) and physical condition of goods and time of receipt;
- for outgoing goods: type of shipping indicators used (if any), status of product-based time-temperature indicators (if any) and physical condition of goods and time of dispatch.

Monitor, record, and investigate discrepancies.

Reason: To demonstrate that TTSPPs have been correctly distributed and to facilitate product recalls and detect theft and fraud.

9. General procedures and record-keeping

9.1 Emergencies and contingency planning

Make contingency arrangements for the safe storage of TTSPPs in the event of emergencies, including, but not confined to:

- extended power supply outages;
- equipment failure; and
- vehicle breakdown during transport of TTSPPs.

Prepare action plans to deal with products subjected to temperature excursions.

Ensure that the responsible staff know, and have rehearsed, the appropriate actions to be taken in the event of the identified emergency scenarios.

Reason: Loss prevention.

9.2 General record-keeping

9.2.1 Record-keeping

Maintain comprehensive records and ensure that they are laid out in an orderly fashion and are easy to check.

Paper records must be:

- stored and maintained so that they are accessible and easily retrievable;
- labelled, dated and filed for easy identification;

- protected against deterioration and loss due to fire, flood or other hazards;
- kept secure and protected against unauthorized access; and
- signed and dated by authorized persons and not changed without due authorization.

Computer records must be:

- logically filed for easy identification and retrieval;
- kept secure and protected against unauthorized access;
- where feasible, manually signed, dated and scanned or when electronically archived dated, encrypted and with check-sum,¹⁵
- regularly backed-up and archived on media that are independent of the record-keeping computer system(s). Back-up media may be a separate secure server, a separate hard disc, a flash drive or other digital media appropriate to the scale of the operation.

9.2.2 Content of records

Ensure that the following traceability data is recorded for each TTSPP batch number, as applicable:

- status of product on arrival;
- temperature and humidity records including records of excursions outside labelled storage and/or transit temperature specification conditions;
- general TTSPP stock transactions, including purchase and sale records;
- controlled drug audits;
- audits for products with high illicit value;
- audits for hazardous products;
- stock tracking;
- return, recall, withdrawal and disposal reports, where relevant;
- product complaint reports, where relevant; and
- counterfeit product reports, where relevant.

Maintain all records in accordance with local legislation and regulations.

¹⁵ Electronic records from data loggers are usually encrypted and protected by check-sums. This ensures compliance with FDA Title 21 CFR Part 11:Electronic Records; Electronic Signatures; Final Rule (1997).

9.2.3 Record review and retention

Ensure that records are reviewed and approved on a regular basis by a designated member of the quality management team. Ensure that records are accessible for review by end-users, the regulatory authority and other interested parties. Retain records for the minimum period required under local legislation, but for not less than three years.

Reason: Internal quality control, transparency and external inspection by the regulatory authorities and other interested parties.

9.3 Temperature and humidity records

9.3.1 Temperature records

Monitor and record storage temperatures in all temperature-controlled rooms, cold rooms, freezer rooms, refrigerators and freezers, as follows:

- Check and record temperatures at least twice daily — in the morning and evening — and preferably continuously.
- Review temperature records monthly and take action to rectify systematic excursions.
- Systematically file temperature records for each storage environment or piece of equipment to ensure traceability. Keep records for at least one year after the end of the shelf-life of the stored material or product, or as long as required by national legislation.

9.3.2 Humidity records

When storing products which are adversely affected by high relative humidity (see clause 4.5.3), monitor and record humidity levels in all temperature-controlled rooms as follows:

- Record humidity at least twice every 24 hours or preferably continuously.
- Check humidity records daily.
- Review humidity records monthly and take action to rectify systematic excursions.
- Systematically file humidity records for each temperature-controlled room to ensure traceability. Keep records for at least one year after the end of the shelf-life of the stored material or product, or as long as required by national legislation.

Reason: Internal quality assurance and availability of records for review by the regulatory authorities and other interested parties.

10. Environmental management

10.1 Normative references

- ISO 14001: 2004. *Environmental management systems — Requirements with guidance for use.*
- *The Montreal Protocol on Substances that Deplete the Ozone Layer.* UNEP, 2000.

10.2 Environmental management of refrigeration equipment

Ensure that all new refrigeration equipment for temperature-controlled storage and transport is specified to:

- use refrigerants that comply with the Montreal Protocol;
- minimize or eliminate the use of refrigerants with high global warming potential (GWP); and
- minimize CO₂ emissions during operation.

Select equipment to minimize whole-life environmental impact and employ best practice to eliminate leakage of refrigerant into the environment during installation, maintenance and decommissioning of refrigeration equipment.

Reason: Compliance with international protocols and accords on climate change and environmental protection.

11. Quality management

11.1 Normative references

- ICH, 2005: *ICH Harmonized Tripartite Guideline: Quality risk management Q9*
- ISO 9000:2005. *Quality management systems — Fundamentals and vocabulary*
- ISO 9001:2008. *Quality management systems — Requirements*
- ISO 9004:2000. *Quality management systems — Guidelines for performance improvements*
- ISO 10005:2005. *Quality management systems — Guidelines for quality plans*
- ISO 19011:2002. *Guidelines for quality and/or environmental management systems auditing*

11.2 Organizational structure

Establish, document and maintain an organizational structure for the TTSPP storage and shipping and distribution operations which clearly identifies all key management responsibilities, and the personnel who are accountable.

Reason: Quality management.

11.3 Quality systems

11.3.1 Quality system

Establish, document and maintain a quality system for the management of TTSPPs including, the following, as applicable:

- standard quality system(s) and associated auditing procedures;
- written procedures and specifications;
- record storage, record retention and record destruction programme;
- risk management;
- calibration programme;
- stability programme;
- qualification and validation programme;
- deviation and root cause investigation programme;
- corrective and preventive action (CAPA) procedures;
- training programme;
- periodic temperature-controlled process assessment;
- change control programme;
- maintenance programme;
- management controls;
- product return and recall/withdrawal policies, including emergency recalls;
- product complaint policies;
- material destruction programme;
- warehouse and storage programme;
- shipping and distribution programme;
- notification systems for regulatory agencies; boards of health and ministries of health; and
- self-inspection programme and continuous quality improvement.

Carry out annual reviews of the quality management system to ensure that it remains appropriate, relevant, and effective.

Reason: Quality assurance.

11.3.2 Self inspections

Conduct regular self-inspections to ensure continuing compliance with quality management standards GSP and GDP; record results, follow-up with the corrective actions needed to rectify areas of non-compliance and document the changes made.

11.3.3 Contractors subject to service level agreements

Ensure that every contractor with whom there is an SLA provides periodic evidence of compliance with the GSP and/or GDP standards incorporated into the SLA.

Reason: To demonstrate compliance with applicable quality management standards.

11.4 Management of documents and standard operating procedures

11.4.1 Standard operating procedures

Develop and maintain SOPs covering correct storage, internal shipping and external distribution of TTSPPs, including, but not limited to, the following topics:

- security, including management of controlled and hazardous TTSPPs;
- safe handling of TTSPPs;
- temperature monitoring;
- calibration of temperature and humidity monitoring devices and alarm systems;
- qualification and validation procedures, including temperature mapping;
- maintenance of controlled-temperature equipment;
- facility cleaning and pest control;
- facility maintenance;
- product arrival (receiving) procedures and records;
- stock storage and warehousing procedures (put away, replenishment, order fulfilment, packing);
- stock control procedures and records;
- distribution procedures and records;
- management of temperature excursions;

- product return and recall/withdrawal procedures and records;
- product complaint procedures and records;
- safe disposal of damaged, expired and quarantined products and records which are no longer required;
- temperature-controlled packaging and route qualification;
- temperature-controlled vehicle operation, including management of security locks and seals;
- emergency response procedures; and
- environmental management.

Ensure that all documents are clear and unambiguous and that document change control procedures are in place as specified in clause 11.5.

Reason: Quality management and staff training.

11.5 Document control

Ensure that all quality manuals, SOPs and similar documents are:

- authorized by an appropriate person;
- recorded in a document register;
- regularly reviewed and kept up to date, with all changes recorded and authorized;
- version controlled;
- issued to all relevant personnel; and
- withdrawn when superseded.

Withdraw superseded documents and retain record copies for document history files and for the minimum period(s) required by the regulatory authorities and for duty-of-care purposes.

Reason: Good quality management practice.

12. Personnel/training

12.1 Training

12.1.1 General training

Provide regular and systematic training for all relevant personnel responsible for storage, loading and unloading areas used for non-hazardous TTSPPs, covering the following:

- applicable pharmaceutical legislation and regulations;
- SOPs and safety issues; and
- response to emergencies.

Ensure that each employee understands his or her specific responsibilities. Provide similar training for drivers who are responsible for transporting these substances. Maintain individual training records to demonstrate compliance and regularly evaluate the effectiveness of training programmes.

Reason: To ensure that all relevant personnel are competent to carry out their duties.

12.1.2 Specialist training

In addition to the training described in clause 12.1.1, provide regular and systematic additional training for relevant personnel responsible for storage, loading and unloading of controlled or hazardous TTSPPs. Training should cover the following:

- applicable legislation and regulations;
- security and safety risks; and
- response to emergencies.

Ensure that each employee understands his or her specific responsibilities. Maintain training records to demonstrate compliance and perform effectiveness checks on training. Provide similar training for drivers who are responsible for transporting these substances.

Reason: To ensure that all relevant personnel are competent to handle controlled or hazardous TTSPPs.

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4.16 Technical supplements to Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products

Annex 9, WHO Technical Report Series, 961, 2011

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1. The technical supplement series

This series of technical supplements has been written to amplify the recommendations given in *Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products* (WHO Technical Report Series, No. 961, 2011, Annex 9).¹ This document sets out the principal requirements for the safe storage and distribution of time- and temperature-sensitive pharmaceutical products (TTSPPs).

The introduction to the guidance documents states that: "... supplementary materials will be developed to show how the requirements can practically be achieved, particularly in resource constrained settings." The technical supplements, which make up this volume, are intended to provide this additional material; each one is linked back to a specific clause or clauses in the parent document. All 16 documents are written in a standard format and each contains a reference section with hyperlinks to relevant supporting materials. Most of these materials are available free online. References to print publications are minimized to avoid the difficulties associated with purchasing books and journals.

1.1 Topics covered

Table A5.1 lists the titles of the supplements and the model guidance sections to which each one refers.

Table A5.1

Titles of supplements and model guidance section to which each refers

Title	Section(s)
1. Selecting sites for storage facilities	Section 2
2. Design of storage facilities	Section 2 to 5
3. Estimating the capacity of storage facilities	Section 3.1 to 3.4
4. Security and fire protection in storage facilities	Section 3.7
5. Maintenance of storage facilities	Section 3.10
6. Temperature monitoring of storage areas	Section 4.5.2, 4.5.4
7. Qualification of temperature-controlled storage areas	Section 4.7
8. Temperature mapping of storage areas	Section 4.7

¹ http://www.who.int/medicines/areas/quality_safety/quality_assurance/ModelGuidanceForStorageTransportTRS961Annex9.pdf?ua=1.

Table A5.1 continued

Title	Section(s)
9. Refrigeration equipment maintenance	Section 4.9
10. Checking the accuracy of temperature control and monitoring devices	Section 4.10
11. Qualification of refrigerated road vehicles	Section 6.4, 6.5
12. Temperature-controlled transport operations by road and by air	Section 6.5, 9
13. Qualification of shipping containers	Section 6.8.1 to 6.8.4
14. Transport route profiling qualification	Section 6.8.3, 6.8.4
15. Temperature and humidity monitoring systems for transport operations	Section 6.5, 9
16. Environmental management of refrigerant gases and refrigeration equipment	Section 10.2

1.2 Target readership

The target readership for the model guidance, and for the technical supplements, includes regulators, logisticians and pharmaceutical professionals in industry, government and international agencies.

1.3 Document development and review process

The technical supplements have been written by specialist authors. All 16 supplements passed through the following editorial and public review process.

1. Each document was prepared over the course of several drafts in consultation with the series editor.
2. Acronyms and glossary definitions were harmonized throughout.
3. Public consultation drafts were posted on the WHO website in mid-2014. Review comments were received from a number of people and organizations.
4. Reviews were consolidated by the series editor and sent to the individual authors for initial comment.
5. Amended documents were prepared containing the consolidated comments categorized as “accepted”, “rejected” and “for discussion”. These new drafts were sent back to the individual authors for further comment.

6. The series editor prepared final drafts based on the authors' responses and these drafts were checked, reviewed and signed off.
7. On the basis of these final comments, clean versions were prepared for review by the Expert Committee on Specifications for Pharmaceutical Preparations and by the Expert Committee on Biological Standardization.

On the following pages, the contents pages of the 16 technical supplements are reproduced. The full texts will be made available in electronic form on the CD-ROM of *Quality assurance of pharmaceuticals* (2015 and updates) and on the website.²

² <https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/>.

Supplement 1

Selecting sites for storage facilities

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-trsno-961>

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 - 2.4.6 *Assess flood risks*
 - 2.4.7 *Assess weather and climate-related risks*
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 - 2.4.9 *Assess other natural hazards*
- 2.5 Detailed site investigation: identifying risks and opportunities
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 - 2.5.7 *Low carbon energy potential*
 - 2.5.8 *Environmental impact assessment*

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Supplement 2

Design and procurement of storage facilities

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-a-trs-961>

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Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-b-trs-961>

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Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-c-trs-961>

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Maintenance of storage facilities

Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

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Technical supplement to

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This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-e-trs-961>

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Supplement 7

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Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

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<https://www.who.int/publications/m/item/Annex-9-f-trs-961>

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Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

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Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-h-trs-961>

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Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-i-trs-961>

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Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-j-trs-961>

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Technical supplement to

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This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-k-trs-961>

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This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-l-trs-961>

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Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-m-trs-961>

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Technical supplement to

Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (WHO Technical Report Series, No. 961, 2011), Annex 9.

This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-n-trs-961>

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Technical supplement to

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This supplement is available at:

<https://www.who.int/publications/m/item/Annex-9-o-trs-961>

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Annex 1, WHO Technical Report Series, 1010, 2018

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1. Introduction

1.1 Background to development of guidelines

1.1.1 Needs

Over the past three decades, there has been a constant, and at times, exponential growth in global interest in the use of herbal medicines. This increase in popularity and usage of herbal medicines is evident in the global market. Herbal medicines, including finished herbal products and the starting materials for their production, such as medicinal plants, herbal materials, herbal preparations and herbal dosage forms, are moving into international commerce and global trade, which reflects their increased economic value and importance.

Adverse events reported to the regulatory authorities in relation to the use of herbal products are often attributable to poor quality of source material and manufacturing and processing factors, among others. Correct identification of source plant species and the selection of appropriate parts for use in herbal medicines are basic and essential steps for ensuring safety, quality and efficacy of herbal medicines. Hence, the safety and quality of herbal medicines at every stage of the production process have become a major concern to health authorities, health care providers, the herbal industries and the public.

The safety and efficacy of herbal medicines largely depend on their quality. Unlike pharmaceutical products formulated from single-molecule chemicals produced synthetically or by isolation from natural source materials employing reproducible methods, herbal medicines consist of simple processed herbs or finished herbal products prepared from source materials containing a multiplicity of chemical constituents, the quality and quantity of which can vary from batch to batch due to intrinsic and extrinsic factors. Consequently, the quality of finished herbal products is greatly influenced by the quality of the raw materials and the intermediates; and the requirements and methods for quality control of finished herbal products, particularly for mixed herbal preparations, are far more complex than those employed for single-molecule chemical medicines.

A number of World Health Assembly (WHA) resolutions relating to traditional medicine have requested the World Health Organization (WHO) to provide technical support to develop methodology to monitor or ensure the safety, quality and efficacy of herbal medicines. The International Conferences of Drug Regulatory Authorities, and annual meetings of International Regulatory Cooperation for Herbal Medicines, as well as the Meetings of the National Centres Participating in the WHO International Drug Monitoring Programme have also requested WHO to develop and continuously update the technical guidelines on quality, safety and efficacy of herbal medicines.

1.1.2 Process and context

Participants of the WHO informal meeting on methodologies for quality control of finished herbal products (held in Ottawa, Canada in July 2001) looked at the overall

picture of herbal medicines: from raw materials to the distribution and supply of finished herbal products, including key steps at which quality control is required.

One of the main recommendations of the meeting was that WHO should prepare a series of technical guidelines and documents covering quality control issues (from raw materials to finished herbal products), as well as to update existing documents.

Following the meeting's recommendations, and as a part of the implementation of relevant WHO strategies (notably, WHO traditional medicine strategies and WHO medicines strategies) and WHA resolutions, WHO undertook the development of four new guidelines and updated other existing documents. Their aim is to provide technical guidance on quality control required at key steps in the production of herbal medicines to support Member States in their efforts to ensure the quality of herbal medicines. These guidelines are:

- *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants (1);*
- *WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (2);*
- *WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines (3); and*
- *WHO guidelines on good herbal processing practices for herbal medicines (present document).*

WHO has also updated two key technical guidance documents:

- *WHO good manufacturing practices (GMP): supplementary guidelines for the manufacture of herbal medicines (4), which was also reproduced in WHO guidelines on good manufacturing practices (GMP) for herbal medicines (5) and further updated (6); and*
- *Quality control methods for herbal materials (7), which includes the WHO good practices for pharmaceutical quality control laboratories as an annex.*

1.1.3 Preparation of the guidelines

The original title suggested for these guidelines was “Good processing practices for herbal materials”. The working draft guidelines were reviewed, and the objectives, scope and proposed contents were discussed and agreed to at the second WHO consultation on quality control of herbal medicines (Hong Kong SAR, China in November 2014). The first draft guidelines were drafted and revised twice, through a global review process. The second revised draft was reviewed and discussed at the third WHO consultation on quality control of herbal medicines held in Hong Kong SAR, China, in September 2017. The draft was then further revised based on the discussion and consensus reached at the third WHO consultation.

1.2 Scope

Herbal processing encompasses the unique procedures of preparing herbal materials and herbal preparations, and it may be extended to the production of finished herbal products, with the ultimate goal of assuring herbal medicines quality. Thus, within the context of quality assurance and control of herbal medicines, the *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants* (1) cover the cultivation and collection of medicinal plants, together with certain post-harvest operations in which the concept of “post-harvest processing” is laid down. The good herbal processing practices (GHPP) set out in the present guidelines are intended to complement, and should be used in conjunction with, the GACP guidelines. On the other hand, the *WHO guidelines on good manufacturing practices (GMP) for herbal medicines* (4–6) have established general technical requirements for quality assurance and control in the manufacture of herbal medicines. In general, they cover the production steps following “post-harvest processing”, including steps known as “processing”. The GHPP guidelines are thus intended to supplement technical guidance on processing in the post-harvest stages.

In this scenario, GHPP is integrally linked to GACP and GMP, by elaborating on the post-harvest processing procedures (which are dealt by the former) and supplementing the latter on processing procedures for the production and manufacture of herbal medicines. These guidelines will provide technical guidance on GHPP in the:

- processing of herbs into herbal materials;
- processing of herbal materials into herbal preparations; and
- processing of herbal materials or herbal preparations into herbal dosage forms.

1.2.1 Processing of herbs into herbal materials

The concept of post-harvest processing set out in the GACP encompasses the immediate treatments accorded to herbs obtained from cultivation or field collection to free them from foreign matter, untargeted or extraneous plant materials and other contaminants. Integral to the preparation of herbal materials are the procedures of “inspection” and “sorting”, as well as “primary processing” procedures such as washing, disinfection, primary cutting, cooling, freezing and “drying”. These processes are described in detail in these GHPP guidelines.

In addition, various other “primary processing” procedures are applied to herbs, as a single processing procedure or as combined procedures. These include a well-defined series of procedures intended to alter their toxicity or modify their medicinal activity. These procedures include advanced cutting and comminution (fragmentation), ageing, sweating (fermentation), baking/roasting, boiling/steaming, stir-frying and primary distillation. Technical information on these *primary processing* procedures, applied during the *post-harvest processing* process are also elaborated on in the present GHPP guidelines.

1.2.2 Processing of herbal materials into herbal preparations

The herbal materials described above may be used as herbal medicines. Such (processed) herbal materials intended for direct therapeutic use should be produced under GACP and GMP conditions. In many other cases, herbal materials will undergo further “processing” treatment procedures before being used to manufacture the finished herbal products. The active ingredients are usually processed together with other components of the herbal materials. Sometimes these active ingredients are further concentrated by the removal of inactive and/or undesirable substances. The herbal preparations thus obtained include extracts, decoctions, tinctures, essential oils and others. The processes involved include extraction, distillation, fractionation, concentration, fermentation, or other chemical or biological methods.

General guidelines for good practices in the production of herbal preparations and/or finished herbal dosage forms as set out in the GMP requirements prescribed by WHO guidelines (4–6, 8) should be followed. Technical information on the key processes is supplemented in the present GHPP guidelines.

1.2.3 Processing of herbal materials or herbal preparations into herbal dosage forms

Depending on the intended use, herbal materials could be regarded as starting materials and herbal preparations could be regarded as intermediates in the process of producing finished herbal products, or as herbal dosage forms for therapeutic applications. In the latter case, simple herbal dosage forms may be prepared either from herbal materials (such as unprocessed seeds or plant exudates) or herbal preparations (such as ground powders and dried extracts) ready for administration to patients. These herbal dosage forms, produced under GMP conditions, include decoctions, tea bags, granules, syrups, ointments or creams, inhalations, patches, capsules, tablets and pills, among others. Supplementary technical information on the key processes is included in these GHPP guidelines.

1.3 Objectives of the guidelines

These guidelines will provide technical guidance on GHPP for the production of herbal materials, herbal preparations and, ultimately, herbal dosage forms (guided by GMP). Under the overall context of quality assurance and control of herbal medicines, the main objectives of these guidelines are to:

- provide general and specific technical guidance on GHPP for herbal medicines;
- provide technical information on general as well as specific good herbal processing techniques and procedures applied to the preparation of herbal materials from herbs;

- provide technical information on good herbal processing techniques and procedures applied to the production of herbal preparations from herbal materials;
- provide supplemental technical information on good herbal processing techniques and procedures applied to the production of dosage forms of herbal medicines;
- provide a model for the formulation of national and/or regional good herbal processing practices guidelines and monographs for herbal materials, as well as for herbal preparations, and related standard operating procedures (SOP); and
- contribute to the quality assurance and control of herbal materials, herbal preparations and herbal dosage forms to promote safety, efficacy and sustainability of herbal medicines.

1.3.1 Use of these guidelines

These guidelines should be considered in conjunction with the existing WHO technical documents and publications relating to the quality assurance of herbal medicines and medicinal plants (for details, see references 1–16).

The *WHO guidelines on good herbal processing practices for herbal medicines* is one of a series of guidance documents concerned with control measures necessary to produce quality herbal medicines for safe and efficacious use as directed by the regulatory authority concerned. The present document concerns the assurance of the quality of the herbal materials prepared by various methods and processing steps from the herbs obtained under GACP. It also covers the herbal preparations prepared using various methods and processing steps from the herbal materials, as well the herbal dosage forms produced through various methods and processing steps from herbs, herbal materials or herbal preparations. Herbal materials and herbal preparations can be used directly as herbal medicines (when produced under GMP conditions), or can serve as source materials for the production of finished herbal products in accordance with GMP. These guidelines are applicable to the processing operations from post-harvest to herbal dosage forms. The processing of herbs, herbal materials and herbal preparations should meet all applicable national and/or regional quality standards. Adherence to local legislation, rules and practice in each Member State is mandatory. Each Member State should develop its own national guidelines on GHPP for herbal medicines that are appropriate to the country's situation.

1.4 Definitions of terms

The terms used in these guidelines are defined below. The terms and their definitions have been selected and adopted from other WHO documents and guidelines that are

widely used by WHO Member States, as well as from other reference sources, publication details of which can be found in the reference list. These definitions may differ from those included in national regulations and are, therefore, for reference only.

It should be noted that as a consequence of the various types of “herbal medicines” produced, the same type of material may be classified in different ways (for example, powdered plant material may be both “herbal material” and “herbal preparation” or, in a packed form, “herbal dosage form” or “finished herbal product”).

1.4.1 Terms relating to herbal medicines

Herbal medicines include herbs and/or **herbal materials** and/or **herbal preparations** and/or **finished herbal products** in a form suitable for administration to patients (3).

Note: In some countries, herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (for example, animal and mineral materials, fungi, algae or lichens, among others).

Herbs (16)

Herbs include crude plant materials such as leaves, flowers, fruits, seed, stem wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.

Herbal materials¹ (16)

Herbal materials include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting or stir-baking with honey, alcoholic beverages or other plant materials.

Herbal preparations (16)

Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.

Finished herbal products (3)

Finished herbal products consist of one or more herbal preparations made from one or more herbs (i.e. from different herbal preparations made of the same plant as well as

¹ The participants of the third WHO consultation on quality control, held in Hong Kong SAR, China from 4 to 6 September 2017, recommended that latex and exudates can be included.

herbal preparations from different plants. Products containing different plant materials are called “mixture herbal products”).

Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be “herbal”.

Herbal dosage forms

Herbal dosage forms are the physical form (liquid, solid, semi-solid) of herbal products produced from herbs, with or without excipients, in a particular formulation (such as decoctions, tablets and ointments). They are produced either from herbal materials (such as dried roots or fresh juices) or herbal preparations (such as extracts).

Medicinal plants are plants (wild or cultivated) used for medicinal purposes (1, 4–6).

Medicinal plant materials: see Herbal materials

1.4.2 Terms relating to herbal processing practices

Herbal processing

Herbal processing refers to the overall treatment in the course of production of herbal materials, herbal preparations and herbal dosage forms. For the purpose of the present guidelines, herbal processing includes “post-harvest processing” described in the *WHO guidelines on GACP for medicinal plants* (1), as well as “processing” procedures and protocols set out in the *WHO guidelines on GMP for herbal medicines* (4–6, 8).

Post-harvest processing

Post-harvest processing covers any treatment procedures performed on the herbs after harvest or collection when they are being processed into herbal materials. It includes processes such as inspection, sorting and various primary processing and drying. Often, well-defined combined or serial procedures are applied to herbs before they can be used in therapeutic treatment or as intermediates for manufacturing finished herbal products. These treatment processes are considered important pharmaceutical techniques in the herbal industry, through which purity and/or quality of raw herbs is assured (such as prevention of microbial and insect infection or infestation), and the therapeutic properties of raw herbs are altered (such as enhancement of effectiveness or reduction of toxicity). These primary processing procedures may vary from one herbal material to another, depending on its chemical and pharmacological characteristics, as well as the intended therapeutic purposes.

Adjutants

Adjutants are adjunctive substances added during the herbal processing procedures for the purpose of altering the pharmacological or therapeutic properties of the herbal materials, neutralizing or reducing toxicity, or masking the taste, assisting formulation into suitable herbal dosage forms, maintaining stability or extending the storage time. Common adjutants include water, wine, vinegar, honey, milk and clarified butter, among other materials.

1.4.3 Terms relating to quality control

A comprehensive list of terms relating to the quality control of herbal medicines can be found in the *WHO guidelines on GMP for herbal medicines* (5, 6), *Good manufacturing practices for pharmaceutical products: main principles* (8), *Quality control methods for herbal materials* (7), and *WHO guidelines for selecting substances of herbal origin for quality control of herbal medicines* (3). The following terms are more applicable to the present guidelines.

active ingredients refer to constituents with known therapeutic activity, when they have been identified. When it is not possible to identify the active ingredients, the whole herbal medicine may be considered as an active ingredient (3).

batch (or lot)² (5, 8, 17). A defined quantity of starting material, packaging material or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

batch number (or lot number) (5, 8, 17). A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

chemical reference substance (or standard) (17). An authenticated, uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use.

constituents (3). Chemically defined substances or group/group(s) of substances found in a herbal material or herbal preparation.

² The participants at the third WHO consultation on quality control, held in Hong Kong SAR, China from 4 to 6 September 2017, recommended that in case of terminal sterilization, the batch size should be determined by the capacity of the autoclave or any other sterilization equipment.

contamination³ (5, 8, 17). The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.

cross-contamination (5, 8, 17). Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

good manufacturing practice (GMP) (8). GMP is that part of quality management which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial authorization or product specification. GMP is concerned with both production and quality control. GMP is aimed primarily at managing and minimizing the risks inherent in pharmaceutical manufacture to ensure the quality, safety and efficacy of products.

in-process control (5, 8, 17). Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

markers (marker substances) (3). Reference substances that are chemically defined constituents of a herbal material. They may or may not contribute to their therapeutic activity. However, even when they contribute to the therapeutic activity, evidence that they are solely responsible for the clinical efficacy may not be available.

master formula (5, 8, 17). A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

specification (5, 8, 17). A list of defined requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

standard operating procedure (5, 8, 17). An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (for example, equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

³ The participants at the third WHO consultation on quality control, held in Hong Kong SAR, China from 4 to 6 September 2017 recommended that the term "physical" should be added before the term "chemical".

2. Good herbal processing practices for the production of herbal materials

2.1 General information

Post-harvest processing is often specific to the herb and may involve unique procedures. The particular processing method may be a practice based on a tradition as old as the use of medicinal plants, and/or it may be based on proprietary procedures. In either case, herbal processing procedures should be subjected to good practice standards.

Herbs obtained from field collection or cultivation should be subjected to a series of good practice post-harvest processing procedures set out in the GACP guidelines (1). In general, post-harvest processing of herbs includes inspection and sorting, primary processing and drying. The exact herbal processing procedures may vary from one herb to another. Thus, some procedures consist of only a few simple steps of primary processing such as cleaning, primary cutting and sectioning, before being dried. Others may require more complicated steps such as advanced cutting and sectioning (for example, decoction pieces processing), comminuting, ageing, sweating (fermentation), baking/roasting, boiling/steaming and stir-frying, for the purpose of improving the quality, preventing damage from mould and other microorganisms, detoxifying intrinsic toxic ingredients or enhancing therapeutic efficacy. The present GHPP guidelines elaborate and supplement the GACP guidance.

In all cases, good in-process control measures should be employed to assure the quality of the end-product. National and/or regional botanical and chemical quality standards for each processed herbal material should be met. In the absence of national standards, regional or international pharmacopoeial standards may be adopted. Guidance on compliance measures can be found in the annex to the *Quality control methods for herbal materials* (7), WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines (3), WHO guidelines on GACP for medicinal plants (1), WHO guidelines on GMP for herbal medicines (4–6, 8), and the present guidelines.

2.2 Purposes and functions of primary processing

Simple post-harvest processing (such as sorting, washing and leaching) serves to remove dirt and other unwanted materials from the herbs after they have been harvested or collected from the growing site. Unless intended for use in its fresh form, the herb is subjected to a drying procedure, immediately or shortly after harvesting, in order to minimize damage from mould and other microbial infestation.

Through experience gained over the centuries, knowledge has been acquired for the development of various primary processing procedures for maximizing the quality and therapeutic value of herbal medicines. The final form of a herbal material depends upon the nature of the herb and its intended use. In general, primary processing of herbs

serves several purposes, such as concentrating the ingredients; removing undesirable substances; modifying the therapeutic properties; reducing toxicity; facilitating dispensing, compounding and storage. The major objectives of primary processing of herbal materials are summarized below.

2.2.1 Neutralization of toxicity and diminishing side-effects

Herbal materials that possess significant toxicity, highly potent pharmacological activity or are known to cause severe side-effects, should be pretreated in specific manners in order to neutralize the toxicity or to reduce the side-effects prior to use. Such a detoxifying process is particularly important for those herbs that are known to contain toxic or undesirable chemical components; they must be properly processed to remove those unwanted substances. Through the primary processing processes such as steaming and frying, heat-sensitive toxic components will be degraded. In other cases, processes such as sweating (for example, fermentation) and ageing result in enzymatic degradation of the toxic ingredients. For example, raw aconite (*Aconitum carmichaelii* Debeaux or related species) root, containing significant amounts of toxic alkaloids such as aconitine, must be boiled or steamed for hours to hydrolyse aconitine into less toxic derivatives. In the case of cascara (*Frangula purshiana* Cooper), the bark that has been collected or harvested should be kept (aged) for at least one year before use. This is to allow oxidation to occur, by which the strongly purgative hydroxyanthracene glycosides are converted to oxidized compounds with lower laxative potencies.

2.2.2 Modification of therapeutic properties

Some herbal materials require primary processing to alter their therapeutic properties. For example, rhubarb (rhizome of *Rheum* spp.) in its raw form possesses purgative action and is useful as a cathartic. After being steamed with wine, however, the purgative action is attenuated and the processed rhubarb can be used for other purposes such as reducing inflammation.

The specific medicinal property of some herbal materials may be changed through primary processing. For example, the unprocessed raw rehmannia (*Rehmannia glutinosa* (Gaertn.) DC.) root is used to treat fever, hypertension and skin eruptions. After being cooked in wine, however, the processed rehmannia is often used for tonic and anti-ageing purposes in some traditional medicine contexts.

In the case of ginseng (*Panax ginseng* C.A. Mey.) roots, different primary processing procedures give rise to several processed products, such as white ginseng and red ginseng. White ginseng is the herbal material dried in the sun or by heat, whereas red ginseng is prepared through a series of steaming and cooking steps. These two types of ginseng products have different therapeutic uses in some traditional medicine contexts, red ginseng being more potent than white ginseng in its warming or energizing effects.

2.2.3 Enhancing efficacy and reinforcing therapeutic effects

The therapeutic efficacy of certain herbal materials can be augmented through primary processing in some traditional medicine contexts. For instance, the pain-relieving property of corydalis (*Corydalis yanhusuo* W.T. Wang) rhizomes is believed to increase when they are stir-fried with rice vinegar.

2.3 Post-harvest processing procedures

Raw herbs should be inspected and sorted immediately following harvest or collection. They are then subjected to a series of on-site primary processes, and in most cases, subjected to further processes at a processing facility. The exact processing methods may differ from one herb to another, and the guidelines therefore may need to be adjusted on a case-by-case basis.

An example of a model format for a GHPP monograph/SOP protocol is given in Appendix 1.

2.3.1 Sorting (garbling)

The sorting process serves as the first step to ensuring the purity and cleanliness of the herbs. After the bulk amount of the desired plant part has been harvested or collected, all extraneous and unwanted matter including dirt (for example, soil, dust, mud and stones), impurities (for example, insects, rotten tissues, untargeted/extraneous medicinal plant(s) and/or plant part(s)), and residual non-medicinal as well as toxic part(s) must be removed from the medicinal part(s). Depending on the herb, the process may involve procedures such as:

- removing dirt and foreign substances;
- discarding damaged parts;
- peeling (to separate unwanted plant part(s) from the medicinal plant part(s) such as removing unwanted root bark from the roots or collecting stem bark from the stem);
- sieving, trimming, singeing (to remove hairs or rootlets);
- removal of residues of unwanted plant part(s) (for example, removing unwanted seeds from fruits and stripping leaves from stems).

Although in some cases sorting may be done by mechanical means, it is usually done by hand. Only staff who are suitably trained and equipped (for example, wearing gloves and a dust mask, etc. as appropriate) should carry out this work.

2.3.2 Primary processing

Washing

Raw herbs, especially roots, rhizomes and tubers, are usually washed with clean water and dried soon after harvest or collection. During the washing process, scraping and brushing may be necessary. It is generally recommended not to soak the herbs in water for an unnecessarily long period. Water should be changed as frequently as required. The use of water containing a low concentration of chlorine (for example, sodium hypochloride, bleach) to prevent microbial fermentation is recommended where and when possible or practical.

Leaching

Some impurities can be removed by the action of running water over the raw herbs (leaching). The duration of leaching has to be controlled in order to prevent excessive loss of active ingredients.

Primary cutting

Bulky raw herbs that have been harvested or collected may require primary cutting to reduce their size before transportation to the processing or manufacturing facility. Primary cutting is usually performed at or near the harvest or collection site.

Ageing

The ageing process refers to storing the herbal materials for a period of time after harvesting or collection from the field prior to use. Herbs are generally aged in the sun or in the shade, depending on the specific herbal material. During the process of ageing, excessive water is evaporated and enzymatic reactions (such as hydrolysis of the glycone portion of glycosides) or oxidation may occur to alter the chemical composition of the herbal material. For example, in cascara (*Frangula purshiana* Cooper) bark, after proper ageing (at least one year, or having been artificially heated to speed up the process), the reduced forms of the emodin glycosides in the fresh bark are converted to monomeric oxidized emodin glycosides. The latter form of glycosides are milder cathartic agents, with reduced irritating effects that may cause vomiting and stomach upsets, and hence, are more suitable as a therapeutic agent.

Sweating

A similar process known as sweating (for example, fermentation) involves keeping the herbal materials at a temperature of 45–65 °C in conditions of high humidity for an extended period, from one week to two months, depending on the plant species. The sweating process is considered a hydrolytic and oxidative process in which some of the chemical ingredients within the herbal materials are hydrolysed and/or oxidized.

The herbal materials are usually densely stacked between woollen blankets or other kinds of cloth. For example, vanilla beans (*Vanilla planifolia* Jacks. ex Andrews) are well known to undergo repeated sweating between woollen blankets in the sun during the day and packed in wool-covered boxes at night for about two months. During this process, the vanilla pods lose up to 80% of their weight and take on the characteristic colour and odour of vanilla.

Parboiling (blanching)

After washing, certain herbal materials may undergo a parboiling or blanching process in which they are put into boiling water for a brief period without being fully cooked. Such a heating procedure may serve several purposes, such as improving storage life of the processed materials by gelatinizing the starch, preventing mould or insect contamination, easily drying, destroying enzyme activity to prevent the alteration of certain chemical constituents, and facilitating further processing such as removal of the seed coat of almonds.

Boiling or steaming

The boiling process involves cooking the herbal materials in water or another liquid such as vinegar, wine, milk or other vehicle.

In the steaming process, herbal materials are kept separate from the boiling water but have direct contact with the steam, resulting in a moist texture of the herbal materials. Often, the herbal materials are placed in a steamer or in a special utensil equipped with a flat frame suspended over boiling water. In some cases, the herbal materials are pre-mixed with excipient substances such as wine, brine or vinegar before being steamed. The boiling or steaming process serves to soften plant tissues, to denature enzymes present in the herbal materials, and/or to thermally degrade selected chemical constituents. At the same time, the excipient, if used, is absorbed into the plant tissues to become an integral part of the processed herbal materials. For example, *Reynoutria multiflora* (Thunb.) Moldenke (synonym *Polygonum multiflorum* Thunb.) root is often steamed in the presence of a black bean (*Phaseolus vulgaris* L.) decoction in order to enhance its tonic effects. Boiling the raw herbs such as *Croton tiglium*, *Abrus precatorius*, *Nerium oleander* and *Gloriosa superba* L., in cow's milk is practised in some traditional medicine contexts to reduce the levels of their toxic ingredients and thus diminish the toxicity of the herbal materials.

Baking or roasting

The baking or roasting process is a dry-heating using indirect, diffused heat, where the herbal materials are put in a heating device. The herbal materials are often embedded in bran or magnesium silicate (talc) powder to ensure even heating over the entire surface at an elevated temperature for a specified period of time. Some herbal materials are wrapped in moistened papers during the roasting process. The exact temperature used

and duration of baking or roasting vary from one herbal material to another. Some are baked or roasted until the surface colour turns yellowish brown; some may be further heated until charred. For example, nutmeg (*Myristica fragrans* Houtt.) and kudzu (*Pueraria montana* var. *lobata* (Willd.) Sanjappa & Pradeep) root require roasting before they are used for medicinal purposes.

Stir-frying

Stir-frying is a process in which the herbal materials are put in a pot or frying pan, continuously stirred or tossed for a period of time under heating until the external colour changes, charred or even carbonized. Depending on the plant species, the stir-frying process may require the addition of adjuvants such as wine, vinegar, honey, saline and ginger juice, which would be infused into the herbal matrix to become an integral part of the processed herbal material.

To ensure even heating over the surface of the herbal materials, sand, rice, bran, talc or clay can be admixed with the herbal material during stir-frying.

For example, liquorice (*Glycyrrhiza glabra* L. and *G. uralensis* Fisch.) root and rhizome and Astragalus roots (*Astragalus mongolicus* Bunge or *A. membranaceus* (Fisch.) Bunge) are often stir-fried with honey for the preparation of decoction slices, whereas the *Salvia miltiorrhiza* Bunge root is stir-fried with wine. Fresh ginger is often stir-fried with sand until the surface colour turns brown. In other instances, ginger can be further stir-fried over intense fire to a carbonized state for use as decoction pieces.

Fumigation

Fumigation with sulfur dioxide has been employed in post-harvest handling of some herbs for the purpose of preserving colour, improving fresh-looking appearance, bleaching, preventing the growth of insects and inhibiting decay caused by moulds. Thus, the process has been frequently applied to herbal materials of light and bright colours to avoid “browning”. Due to concerns about the undesirable residues, this process should be avoided as far as possible. When a real need is identified, treatment should be carried out at the earliest possible stage and exclusively by adequately trained and qualified personnel, according to the specific recommendations for use. All relevant regulations (for example, limits on sulfite residue) should be complied with.

Irradiation

In some cases, irradiation or ultraviolet light can be used to eliminate or reduce microbial load of the herbal materials. The use of these procedures has to comply with the national and/or regional regulations.

Advanced cutting, sectioning and comminution

When thoroughly dried, the herbal materials are processed by cutting and sectioning into convenient or specific sizes and shapes or forms for storage, direct use as decoction

slices or pieces, and/or for further processing for the manufacture of herbal preparations or herbal dosage forms. Decoction slices or pieces are available in many Member States for direct use as herbal medicines. Where applicable, the entire, sectioned or cut herbal materials are comminuted or pulverized into powder form in accordance with common herbal medicines practice, for use as herbal dosage forms.

White and/or red ginseng products presented as root pieces, slices or in powder form prepared from appropriately dried roots of *Panax ginseng* C.A. Mey., marketed as herbal medicines, are good examples of herbal materials derived from simple processing procedures.

Other primary processing procedures

Other primary processing procedures may be applied to raw herbs at an early stage for the production of herbal materials, such as collection of gums or resins. Also included under the term primary processing are primary distillation of raw herbs to obtain crude essential oils and expression to obtain fresh juice. Such procedures are usually performed in the processing facility under GMP conditions.

2.3.3 Drying

Unless used in the fresh state, the raw herbal materials need to be dried after being sorted and washed. In general, they must be dried as soon as possible to protect them from mould and other microbial infestation. Drying will also prevent tissue deterioration and phytochemical alteration caused by the actions of enzymes and microbial organisms. It will also facilitate grinding and milling, and converts the herbal materials into a convenient form for further processing. However, attention must be given to the potential loss of volatile (for example, essential oil) constituents present in the fresh material.

The final moisture content for dried herbal materials varies depending on the tissue structure, but should ideally be below 12%. Information on the appropriate moisture content for a particular herbal material may be available from pharmacopoeias or other monographs.

Proper drying involves four major aspects: control of temperature, humidity, airflow and cleanliness of the air. The drying conditions are determined by the nature of the raw medicinal plant material to be dried (tissue structure and chemical composition) and by the desired appearance of the final form. The drying method used may have considerable impact on the quality of the resulting herbal materials. Hence, the choice of a suitable procedure is crucial. Information on appropriate drying methods and procedures for particular herbal materials may be available from pharmacopoeias or other authoritative monographs. Raw herbal materials are most often dried by sun-drying, shade-drying or by artificial heat.

The drying conditions chosen should be appropriate to the type of the herbal material. They are dependent on the characteristics (for example, volatility and stability)

of the active ingredients and the texture of the plant part collected (for example, root, leaf or flower). Generally, one of the following drying processes can be adopted.

Sun-drying

Some herbal materials can be dried in the open air under direct sunlight, provided the climate is suitable. The duration of the drying process depends largely on the physical state of the herbal material and the weather conditions.

For natural drying in the open air, medicinal plant materials should be spread out in thin layers on drying frames and kept away from sources of possible contamination such as vehicle exhaust, heavy dust and rain. They should also be protected from insects, rodents, birds and other pests, livestock and domestic animals. The material should be turned periodically to achieve uniform drying. The drying frames should generally be set up at a sufficient height (for example, 15 cm) above the ground. Efforts should be made to achieve uniform drying within the shortest possible time to avoid mould formation.

Shade-drying

Herbal materials can be dried in the shade with or without artificial airflow to avoid direct exposure to strong sunlight. The drying process is slow, but it is preferred when it is necessary to maintain (or minimize loss of) colour of leaves and flowers. Low temperatures (relative to heat-drying) will also preserve most of the volatile and aromatic components by reducing evaporation.

Drying by artificial heat

Drying by artificial heat can be faster than open-air drying and is often necessary on rainy days or in regions where the humidity is high. Drying of herbal materials may be done using ovens, stoves, rack dryers, solar dryers, tunnel dryers, belt dryers, other heating devices or open fires. The use of an open fire should be avoided as much as possible, as residues of combustion may introduce contamination. When an open fire is used, the area must be well ventilated.

For artificial heat-drying, the temperature, humidity and other conditions should be governed by the physical nature of the herbal material being dried and the physical/chemical properties of its active ingredients. Over-heating may lead to an excessive loss of the volatile components and/or decomposition of chemical constituents. In general, the temperature should be kept below 60 °C for bark and root and below 40 °C for leaves, herbs and flowers.

2.4 General issues

2.4.1 Selection of processing method

Herbal materials derived from the same species but processed by different methods may show significant differences in quality and therapeutic properties, owing to the influence of the treatment process on the chemical composition.

It is not uncommon to find different processing methods being used for the same herb or herbal material, depending on intended use. For example, raw (unprocessed) liquorice is used as an antitussive and expectorant; but after being stir-fried with honey or ghee, the processed liquorice becomes a tonic drug to be used for replenishing body strength.

Prior to processing, it is important to consult the national or regional regulatory standards and other literature sources to decide on the most appropriate method to use. Once a method has been adopted, adherence to the SOP is necessary to ensure batch-to-batch consistency. For industrial production, method validation should be adopted as part of the SOP.

Only suitably trained staff should carry out the work, which should be conducted in accordance with the SOP and national and/or regional regulations in the countries where the plants are grown/collected and manufactured and in which the end-users are located.

2.4.2 Temperature

With in-processing procedures that involve heating, the temperature used is critical. It is necessary to ensure that the required temperature is achieved during the process. In some cases, preheating the equipment (for example, oven, frying pan and steamer) and/or the additives (such as sand, bran and rice) is required before putting in the herbal materials. When heating equipment is used, it should be regularly calibrated.

2.4.3 Duration of procedure/treatment

It is also critical to control the duration of the procedure or treatment of the herbal materials. Both over- and under-treatment will affect the quality of the resulting materials. Duration of the procedure or treatment should be monitored through adequate in-process controls performed on the basis of organoleptic alterations (such as changes in colour, odour, taste and texture) or changes in the contents of active chemical constituents with appropriate instruments or testing.

2.4.4 Use of adjuvants

Common adjuvants used during the processing procedures include water, wine (for example, rice wine, wheat wine and sorghum wine), vinegar, honey, ginger juice, liquorice extract, ghee, brine and so on. Under special circumstances, other adjuvants such as cow's milk, goat's milk, animal bile, goat fat, cow's urine, butter, black bean extract, coconut water, tamarind juice, turmeric, lemon juice and mineral materials (for example, borax) have been used.

The quality of adjuvants must be clearly defined and controlled (according to pharmacopoeial and/or relevant regulatory requirements). The exact amounts and quality of these adjuvants used (the ratio of herbal material and the adjuvant) should

also be consistent from batch to batch. In addition, the use of any materials derived from animals or animal products in any processing procedures should be evaluated for safety and contamination, especially with pathogens, prior to use. General guidance is available in *Safety issues in the preparation of homeopathic medicines* (9).

2.5 Documentation

All processing procedures that could affect quality and safety of herbal materials should be documented. Guidance for good documentation can be found in *Good manufacturing practices for pharmaceutical products: main principles* (5, 8, 17), as well as *WHO guidelines on good agricultural and collection practices for medicinal plants* (1). Thus, it is important to establish a record-keeping system so that all records are up to date, maintained and traceable for the entire processing procedures for each batch of herbal materials.

Written processing records should include, but not be limited to, the following information:

- name of herbal material – botanical name (binomial – genus, species, with the authority (abbreviations, if used, should follow internationally accepted rules)) and the plant family name of the medicinal plant are essential. If required by national legislation, synonyms and applicable subspecies, variety, cultivar, ecotype or chemotype should be documented; if available, the local and English common names should also be recorded;
- plant part(s) of the medicinal plant or herb;
- stage of vegetative development, for example, flowering and fruiting, vegetative maturation;
- site/geographical location (if possible, based on GPS data,) and time of harvesting/collection;
- state of the medicinal plant or herb (for example, fresh or dried);
- batch number, batch size and any other identification code;
- name of supplier;
- dates of receipt of the material, processing of the material, and completion of the process;
- name of person in charge of the processing, and person in charge of batch release;
- general processes that the plant material has already undergone (for example, drying, washing and cutting, including drying time and temperatures, and size of herbal material);
- gross weight of the plant material before and after processing;
- method used for special processing;

- details of the procedures (master formula), including descriptions of the utensil and equipment used, steps of operation, manufacturer, specification, amount and quality grade of the adjuvant (for example, wine or vinegar) and/or other substances (for example, sand, bran) used, temperature control, length of processing time, after-process steps (for example, cooling, drying, cutting), and other relevant information;
- details of animal-derived materials or adjuvants used and their microbiological certificates, if applicable;
- batch production – detail deviations from or modifications of the master formula;
- in-process control, for example, organoleptic changes of the herbal material before and after processing (such as change in colour, shape, texture, odour and taste);
- quality control parameters, grades and/or specifications, and assay results, where appropriate, of active ingredient(s), markers or chemical reference standard(s);
- storage conditions and containers; and
- shelf life/retest period.

3. Good herbal processing practices for the production of herbal preparations

3.1 General information

The herbal materials described in section 2 of these guidelines may be ready to serve as the starting materials for use as herbal medicines. In some cases, they are cut into sections or ground into powder and used directly as the final dosage form. But often the herbal materials will undergo further treatment processes before being used to manufacture the finished herbal products. The ingredients are usually not purified and the extracts are further concentrated by the removal of inactive and/or undesirable substances.

Herbal preparations are thus obtained by subjecting the herbal materials to treatments such as extraction, distillation, fractionation, concentration, fermentation, or other physicochemical or biological methods. The resulting preparations include extracts, decoctions, tinctures, essential oils and others.

3.1.1 Preparation of herbal materials for processing

- The quality of herbal materials should meet the requirements specified in the national pharmacopoeia or recommended by other documents of the end-user's country.

- Authentication of herbal materials should be performed prior to extraction. Purity (absence of contaminants) should also be ensured.
- Proper documentation on the herbal material should be available as recommended in section 2.5.
- The herbal material should be cleaned, dried (unless fresh material is required), and comminuted into an optimal size for extraction.
- The herbal materials should be processed as soon as possible after arrival at the processing facility. Otherwise they must be properly stored to avoid contamination, damage and deterioration (for example, loss of active constituents).
- All operational steps should be reproducible and performed hygienically, in accordance with the processing SOP.

In general, for processes such as extraction, fractionation, purification and fermentation, the rationale for the guidelines should be established on a case-by-case basis. An example of a model format for a good herbal processing practice monograph/SOP protocol to produce a herbal preparation is given as Appendix 2. General guidance is provided below.

3.2 Extraction

Extraction is a process in which soluble plant chemical constituents (including those which have therapeutic activity) are separated from insoluble plant metabolites and cellular matrix, by the use of selective solvent (which is sometimes called the menstruum). The purpose of extraction of herbal material is to eliminate unwanted materials and to concentrate other chemical constituents in a soluble form. Herbal extracts include liquid (fluid) extracts, soft extracts, oleoresins, dry extracts and others. The herbal preparations so obtained may be ready for use as medicinal agents, or they may be further processed into herbal dosage forms such as tablets and capsules.

Various techniques are used for extraction, including maceration, infusion, digestion, percolation – including hot continuous (Soxhlet) extraction – and decoction. Other extraction techniques can also be applied, for example, heat reflux extraction, counter-current extraction, microwave-assisted extraction, ultrasonic extraction (sonication) and supercritical fluid extraction.

3.2.1 Common methods of extraction

In order to produce herbal preparations of defined quality, the use of appropriate extraction technology, extraction conditions, extraction solvents, ratio between herbal material and solvents, and type of equipment are crucial. Some common methods of extraction are described below.

Maceration

Maceration involves the procedures of mixing the properly comminuted herbal materials with the solvent and allowing the mixture to stand at a certain temperature for a defined period of time, agitating as necessary. During the maceration process, chemical constituents are extracted from the plant tissues through a dissolution process into the liquid solvent. Often the herbal material is put in a container and solvent added until the herbal powder is thoroughly moistened. An additional quantity of solvent is then introduced. The mixture is agitated at regular intervals for a defined period of time, strained, and the marc (the solid material) is pressed, to collect residual extract. All liquids are collected, combined and separated by decantation, centrifugation, straining or filtration. The maceration process may be repeated with fresh solvent if desired. In the process of maceration, the herbal materials are macerated in definite quantities of a solvent (at an optimal ratio of the amounts of herbal material to solvent), for a specified duration of time. Exhaustive bulk extractions via maceration can be quite time-consuming and require large volumes of solvent.

In specific cases, a modified maceration procedure involves pre-soaking the herbal material in water for a period of time to induce fermentation. In other cases, maceration can be performed by gentle heating in order to enhance the extraction efficiency in a process known as “digestion”.

“Sonication-assisted extraction” and “microwave-assisted extraction” are modified methods of maceration, in which ultrasound or microwaves are utilized to enhance the extraction efficiency, to reduce the amount of solvent used, and to shorten the extraction time.

For *sonication*, the herbal material is placed in a container together with a solvent, which is in turn put in an ultrasonic bath. The ultrasound provides sufficient power to break down the cell walls of the herbal material and facilitates the solubilization of metabolites into the solvent. The frequency of ultrasound, length of treatment and temperature of sonication are important factors affecting the extraction yield.

For *microwave-assisted extraction*, the herbal material is placed in a container together with water, or another suitable solvent and subjected to microwave treatment. Heat generated by the microwave energy facilitates the dissolution of compounds from the herbal matrix into the solvent.

Sonication-assisted and microwave-assisted extraction are rarely applied to large-scale extraction; they are used mostly for the initial extraction of a small amount of material.

Infusion

Infusion refers to an extraction procedure in which boiling water is poured on the herb or herbal material to produce a dilute liquid preparation. Typically, the herb or herbal material is allowed to stand for some time (usually 5–20 minutes). Sometimes another

quantity of hot water is added and allowed to stand for additional time. The extracted plant material is removed by straining and the infusion is ready for use. Infusion is commonly employed to make herbal teas.

Percolation

Percolation is the procedure in which the solvent is allowed to continuously flow through the herbal material in a percolator (a vessel with an outflow at the bottom end). Typically, the properly comminuted herbal material is moistened with an appropriate amount of solvent and allowed to stand (macerate) for a few hours before being packed into the percolator. Additional solvent is added to totally wet the comminuted herbal material for some time. The bottom end (valve) of the percolator is then opened (adjusted), with fresh solvent being replenished from the top of the percolator to maintain a steady flow of solvent through the bed of herbal material. The flow rate of the liquid is controlled by adjusting the valve of the outlet. The extraction liquid is collected from the bottom outlet of the percolator. When the process is completed, the marc may be pressed and all liquids pooled to obtain the percolate. In addition to the solvent used for the extraction, the flow rate and the temperature influence the extraction yields and they have to be carefully controlled. Percolation is often used for an exhaustive extraction of the herbs and is applicable to both initial and large-scale extraction. In some cases, the process of percolation can be modified by applying vacuum to increase the flow of solvent.

A special technique of percolation is the “continuous (Soxhlet) extraction” process using the Soxhlet or Soxhlet-like apparatus. Usually, 50–60 cycles are necessary for complete extraction. Due to the continuous extraction, this method is more efficient than simple percolation and consumes less solvent. However, due to continuous heating at the boiling-point of the solvent used, thermolabile compounds may be damaged and/or artefacts may be formed. Besides the laboratory-scale setup for continuous extraction, industrial-scale stainless steel extractors and high-pressure extraction are commonly used in many manufacturing facilities.

Decoction

Decoction is the most common method for making herbal preparations in various traditional medicine contexts. It involves boiling the herbal material in water, during which time the chemical constituents are dissolved or extracted into the hot liquid. This procedure is suitable for extracting soluble and heat-stable active constituents of the herb or herbal material.

Supercritical fluid extraction

Supercritical fluid extraction is a modern technique making use of the solvating property of a fluid in its supercritical state (carbon dioxide is the most common supercritical solvent) to dissolve the chemical constituents in herbal materials. The

density of the supercritical fluid (thus its solvating property) can be adjusted by altering the temperature and pressure, or by the addition of modifiers (for example, ethanol) to change the polarity of the supercritical fluid.

3.2.2 Steps involved in the extraction of herbs and herbal materials

The following steps are generally involved in the extraction procedures.

Comminution, fragmentation, grinding or milling (see also section 2.3.2)

Prior to extraction, the herb is generally dried and reduced to a size of 30–40 mesh sieves (the actual size can be adjusted if necessary). If fresh material is used for extraction, it is necessary to perform extraction as soon as possible after collection to avoid deterioration (microbial fermentation). The purpose of powdering the herbal material is to rupture its tissues and cell structures so that the chemical ingredients are more readily exposed to the extraction solvent. Moreover, size reduction increases the surface area, which in turn enhances the mass transfer of chemical ingredients from plant tissue to the solvent. However, excessive grinding can degrade the herbal material through mechanical heating and oxidation from exposure to air. Further, an excessively fine powder may block the pores of the extraction filter, slowing down or preventing the passage of the filtrate; it may even coalesce in the presence of the extraction solvent to form solid lumps, cakes or bricks, not amenable to being extracted.

Extraction

The extraction process is carried out in the selected solvent at a desirable temperature for an optimal period of time. Depending on the polarity of the desired chemical constituents, water or other solvents can be used, either at room temperature (“cold” extraction) or at an elevated temperature (“hot” extraction).

Sequential extraction with a series of solvents of differing polarity is sometimes done to create a series of extract fractions. In this procedure, the herbal material is subjected to organic and aqueous solvents in a sequence of increasing polarities, for example, n-hexane, dichloromethane, ethyl acetate, water-saturated n-butanol and water. As a result, chemical constituents possessing different polarities are transferred from the herbal material to different solvent fractions according to the principle of “like dissolves like”. For example, the initial step of extraction using non-polar solvents (such as n-hexane or petroleum ethers) removes lipophilic constituents (such as alkanes, fatty acids and sterols) from the herbal material in a process sometimes referred to as “defatting”. The compounds with intermediate polarity (such as flavonoid and quinone aglycones) will dissolve in the medium-polarity solvents (such as dichloromethane and ethyl acetate), whereas more polar compounds (such as glycosides and polyphenols) will be concentrated in the more polar solvents (such as butanol or water). Fractionation as a secondary processing step applied to herbal extracts is described in section 3.4.

Separation techniques

After the completion of extraction, the liquid so obtained is separated from the marc by filtration through a filter cloth or filter-paper to remove any particulate insoluble residues. Other separation techniques, including decantation, centrifugation or straining, may be used depending on the method of extraction and composition of the matrix.

Concentration

The extract is often concentrated by the removal of excessive solvent to a thick concentrated extract or to a solid mass. The concentration procedures may involve evaporation under reduced pressure, freeze-drying or spray-drying.

3.2.3 Common herbal preparations obtained by extraction

The extraction process using suitable solvents can yield herbal extracts of liquid, semi-solid or solid consistency. There are four general categories of herbal extracts, i.e. liquid (fluid) extract, soft extract, oleoresin and dry extract.

3.2.3.1 Liquid (fluid) extract

Liquid (fluid) extract is a liquid preparation of herbal materials obtained using water, alcohol or other extraction solvents. Common preparations include:

- Fluidextract

Fluidextract is an alcoholic liquid extract produced by percolation of herbal material(s) so that 1 mL of the fluidextract contains the extractive obtained from 1 g of the herbal material(s).

- Decoction

Decoction is a water-based herbal preparation made by boiling herbal materials with water, and is commonly utilized in various traditional medicine contexts. In some cases, aqueous ethanol or glycerol can also be used to prepare decoctions. However, decoctions may be prepared by a programmable decocting machine that processes the herbal material at a specific temperature for a specific duration and then dispenses the decoction in hermetically sealed plastic pouches of a specified single-dosage volume that can be refrigerated for subsequent reheating and consumption. The amounts of herbal material and solvent used, as well as the length of the decocting process, should be specified.

- Infusion

Infusion is a dilute solution prepared by steeping the herbal materials in boiling water for a short time. Infusions prepared in edible oil or vinegar are also available.

- Tincture

As a general rule, a “tincture” is an alcoholic or hydroalcoholic extract of a herbal material, typically made up of 1 part herbal material and 5–10 parts solvent (for example, ethanol

or wine). Tinctures can be prepared by extracting herbal materials usually with ethanol of a suitable concentration. The ratio of water to alcohol should be recorded.

- Macerate

Macerate is a liquid preparation prepared by soaking the herbal material(s), reduced to a suitable size, in water at room temperature for a defined period of time, usually for 30 minutes, when not otherwise specified.

3.2.3.2 Soft extract

Soft extract is a semi-solid preparation obtained by total or partial evaporation of the solvent from a liquid extract.

3.2.3.3 Oleoresin

Oleoresin is a semi-solid material composed of a resin in solution in an essential and/or fatty oil obtained by evaporation of the excess solvent.

3.2.3.4 Dry extract

Dry extract is a solid preparation obtained by evaporation of the solvent from a liquid/fluid extract. Dry extract can also be prepared by spray-drying with or without the use of an adsorbent (such as methyl cellulose), or by drying and milling to produce a powder. This may be further processed by compression or with use of a binding agent or granulation liquid to produce multiparticulate granules.

3.2.4 Factors influencing extraction of herbal materials

A number of factors influence the efficiency and reproducibility of the extraction process. Issues to consider include the solvent used to make an extract, particle size of the herbal material, the herb-to-solvent ratio, extraction process used (for example, percolation or maceration), extraction time, temperature and other relevant conditions. All these factors should be optimized and set out in the SOP, and be strictly adhered to.

3.2.5 Selection of extraction methods

- The choice of extraction method is governed by the nature (stability, solubility, structural complexity and other properties of the chemical constituents) and amount of material to be extracted. For large amounts, the feasibility of extracting on a bulk scale should be considered.
- The extraction method should be as exhaustive as possible, i.e. removing as much of the desired chemical constituent as possible from the plant matrix.
- It should be fast, simple, economical, environment-friendly and reproducible.

3.2.6 Extraction conditions and procedures

Solvent

- Depending on the nature of the target compounds or undesirable compounds, an appropriate solvent (or solvent mixture) should be selected. While water has been, and is, most commonly used as a solvent, organic solvents of varying polarities are often used in modern methods of extraction to exploit the various solubilities of phytochemical constituents. For example, an aqueous solution of alcohol (for example, 50–80% aqueous ethanol) can extract the majority of organic chemical constituents from herbal materials. Other solvents may apply for the extraction of specific types of constituents (such as proteins and polysaccharides).
- When selecting a solvent or solvent mixture, the following factors should be considered: solubility of the target compounds, stability and reactivity of the solvent, safety (low toxicity, low flammability, non-corrosiveness), cost, ease of subsequent solvent removal and solvent recovery (low boiling-point), and environmental friendliness.
- Before using a solvent, the safety data sheet⁴ should be reviewed and appropriate protective measures should be implemented. Precautions must be taken to minimize the risk of fire and explosion. Care should be taken to reduce environmental contamination and to protect workers and other people in the vicinity from exposure to chemical hazards.
- Toxic solvents and those that are damaging to the environment, for example, benzene, toluene and carbon tetrachloride, should be avoided. Diethyl ether should also be avoided as it is highly flammable and can lead to the formation of explosive peroxides. The use of chlorinated solvents is discouraged; if used, dichloromethane is preferred to chloroform, the latter being more toxic. Ethanol is preferred over methanol; the latter has higher toxicity.
- Solvents are classified into three classes according to the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH),⁵ with respect to their potential risk as follows:

⁴ United Nations (2015) Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Sixth revised edition. Available at: https://www.unece.org/trans/danger/publi/ghs/ghs_rev06/06files_e.html.

⁵ International Council for Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use. ICH Harmonized Guideline – Impurities: Guideline for Residual Solvents (Q3C (R6) dated October 20, 2016). (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3C/Q3C_R6__Step_4.pdf) accessed on 18 May 2017.

- class 1 (solvents to be avoided such as benzene);
- class 2 (limited toxic potential such as methanol or hexane); and
- class 3 (low toxic potential such as ethanol) (18).
- Solvents of general-purpose grade available in plastic containers are often contaminated by plasticizers, and minimizing contamination is especially important when carrying out bulk extraction requiring large volumes of solvent. It is advisable to distil solvents prior to use.
- The amounts of solvent used must be optimized to ensure batch-to-batch conformity.
- The quality and specification of solvent used should be specified and controlled.
- Solvents should be properly stored in non-plastic containers in a well ventilated, fire and explosion containable area; and protected from direct exposure to sunlight.
- When solvents are recycled, strength and purity must be confirmed prior to reuse. Recycled solvent should be used in the same extraction process only.
- Waste solvents must be disposed of safely and properly. National, local or institutional regulations on waste solvent disposal must be strictly followed.
- Limits for solvent residue in extracts or herbal preparations are important to observe especially when the solvent is not considered safe for general consumption.

Temperature

- To avoid thermal degradation of the chemical constituents, extractions are preferably performed at a temperature below 40 °C, unless evidence is available to support the use of higher temperatures.
- For heat-stable constituents, Soxhlet extraction or decoction can be used. In any case, higher than required temperatures should be avoided.
- Temperature during the entire extraction process should be controlled and recorded.

Length of treatment

- The length of extraction time depends on the purpose for which the extraction is performed and the nature of the active phytochemical constituents. Insufficient time will result in incomplete extraction, but

prolonged extraction will lead to excessive extraction of the unwanted constituents and/or degradation of active chemical compounds.

- The number of repeated extraction cycles required for the complete removal of the desirable chemical constituents is as important as the length of time for each extraction.
- The length of extraction time and the number of cycles should be controlled and recorded.

3.3 Distillation

For the extraction of volatile components of herbal materials, such as essential (volatile) oils, the odorous and volatile principles of plants, techniques such as distillation, expression and enfleurage may be employed. Primary distillation sometime takes place soon after the herb is harvested or collected to obtain crude oils. In other cases, herbal materials are distilled under well-controlled GMP conditions in the manufacturing facility.

Water or steam distillation is a method of choice for extracting volatile ingredients from herbs. In brief, the herbal material is packed in a still, a sufficient amount of water is added and brought to the boil (water distillation). Alternatively, a stream of steam is introduced to the herbal material that has been pre-soaked in water (water-steam distillation), or a stream of steam is introduced to herbal materials without water being added (direct steam distillation).

The method of distillation depends on the condition of the herbal materials. Water distillation can be applied to fresh herbs to avoid steam penetrating into the materials such as rose flowers, while direct steam distillation is often used for fresh or dried herbal materials. Freed from the plant tissue, the essential oil is carried away with the steam. Upon condensation, the water and oil are collected in liquid form, which then separates into two immiscible layers. During the process, the yield of essential oil can be quantified by using appropriate methods such as the Clevenger apparatus.

The yield and quality of essential oil obtained by distillation is affected by the process parameters. It is advisable to define optimal conditions in order to obtain the best results. Among the contributing factors are: mode of distillation, condition of raw herbal materials, loading of herbal materials, steam pressure and temperature and length of time for distillation.

3.3.1 Distillation procedures

- The distillation apparatus must be set up properly and safely according to the manufacturer's instructions.
- Distillation should be carried out in a well-ventilated room.
- Optimum distillation conditions, for example, heating rate, herb/solvent ratio and distilling rate, have to be specified and controlled.

- The equipment used should conform with the official safety standards and all procedures must be conducted in accordance with the operational instructions and safety requirements.
- The water used for distillation should at least comply with local requirements for drinking water.

3.3.2 Other methods

Volatile oils that may be decomposed during distillation can be obtained by expression (mechanical pressing), solvent extraction, supercritical carbon dioxide extraction or by the enfleurage process suitable for delicate flowers.

3.4 Fractionation

Fractionation is a separation process in which a mixture is divided into a number of smaller quantities (fractions) with higher content of target substances (chemical compounds). The crude extracts of herbal materials contain complex mixtures of chemical constituents with diverse chemical and physical characteristics. It is often desirable to divide the chemical constituents into different groups based on their similarities in terms of chemical and physical properties, such as a flavonoid- or alkaloid-rich fraction. Fractional separation of a herbal extract can be achieved by subjecting the extract to a variety of fractionation techniques such as liquid–liquid partition and various forms of chromatography. The method can be applied to produce preparations enriched in active compounds, or to remove inactive and/or toxic constituents.

3.4.1 Liquid–liquid partition

Herbal extracts may be fractionated by dissolving in a suitable solvent, if not already in liquid form, and partitioning with an immiscible liquid. One liquid phase is typically aqueous and the other is an organic phase such as dichloromethane or ethyl acetate. The chemical constituents will separate into the different liquid phases depending on their affinity according to the principle of “like dissolves like”. Manipulations of the pH of the aqueous phase combined with liquid–liquid partitioning can also be employed to separate a herbal extract into basic, neutral and acid fractions.

3.4.2 Chromatography

Further refinement of the extract fractions can be achieved by various chromatographic techniques, of which column chromatography is most commonly employed, particularly in the preparative scale. Column chromatography can be carried out using materials based on different mechanisms. Common modes are adsorption, partition, size exclusion, affinity and ion-exchange. The most frequently used stationary phases (solvents) are silica gel and alumina in adsorption chromatography. In size-exclusion

and ion-exchange chromatography, polymeric gels and ion-exchange resins, respectively, are used. A proper column packed with the appropriate stationary phase and eluted by a mobile phase with suitable elution power is crucial to obtain optimized separation of chemical constituents in the herbal extract.

The counter-current techniques, such as high-speed counter-current chromatography and droplet counter-current chromatography, which also employs a liquid–liquid partitioning mechanism, can also be applied to separating constituents in the herbal extract.

3.4.3 Fractionation procedures

Liquid–liquid partition

- The storage, use and disposal of solvents must be done with care and in conformance with the national, local and institutional regulations.
- Experimental procedures should be carried out in certified facilities with sufficient ventilation and safety measures. Ideally, they should be performed inside fume hoods.

Chromatography

- The choice of stationary phase depends on the polarity, molecular size or the charge of the desired ingredients. It should be supported by a good rationale.
- The choice of mobile phase (solvent system) must be optimized.
- Column operation and development procedures (for example, column length and inner diameter, amount of stationary phase used, column packing, particle or bead size or macropore size, porosity and surface area, phase and support, sample application, elution gradient formation, flow rate, temperature, fraction collection and detection method), should be specified and standardized.

3.5 Concentration and drying

The herbal extracts or fractions enriched in active ingredients are often reduced to produce a more concentrated liquid by the removal of excess solvent. This can be achieved through evaporation or vaporization. Solvent (single) can be recovered and may be reused provided that appropriate quality control is ensured. Mixed solvents are not reusable. The concentration depends on the desired end-product.

Equipment for concentration may include descending film, thin layer or plate concentrators. Any method used to concentrate the extracts must avoid excessive heat because the active ingredients may be heat labile. The liquid preparation so obtained may be used as it is or further processed into a semi-solid or dry extract.

When complete drying is required, the drying process can make use of vacuum freeze-dryers (lyophilizers), cabinet vacuum dryers, continuously operating drum or belt dryers, microwave ovens or atomizers. The choice of technique for drying depends on the stability of the product and the amount of solvent that must be removed. The total removal of solvent results in a dry extract, which may be less susceptible to microbial contamination than liquid extracts. Dry extract powders are often produced by drying the extract onto an inert carrier, such as methyl cellulose, maltodextrin or another excipient fit for the intended purpose, to facilitate processing into the final finished product.

3.5.1 Concentration and drying procedures

- The minimization of loss and/or damage to the chemical constituents of interest is critical to ensuring the effectiveness of the preparation. Therefore, the preservation of the active ingredients is of paramount importance during the concentration stage when heat is often applied to evaporate the solvent. Any concentration process should ensure that minimal thermal decomposition and chemical reactions (such as oxidation) occur. For organic solvents, evaporation under reduced pressure at a temperature below 40 °C is preferred.
- Solvent removal should be done as soon as possible after extraction. Prolonged exposure to sunlight should also be avoided.
- While evaporation is the most common and the most often applied technique for concentration, other approaches such as membrane technology and freeze-drying concentration are available.

3.6 Fermentation

In some cases, a herbal preparation is obtained after undergoing a process of fermentation of the comminuted herbal material or decoction. Fermentation can be either natural (“self-fermentation”) involving microbial cultures already present on the herb, enzymes naturally occurring in the herb (which may be activated by bruising the herb), or both, or by introducing an appropriate microbial organism (for example, *Lactobacillus* bacteria or yeast).

For natural fermentation, the dry comminuted herbal material, a decoction, or an extract of herbal material is often mixed with the juice of sugar-cane, brown sugar or honey and the mixture is kept in an airtight utensil for several weeks for anaerobic fermentation to occur.

In some cases, herbal materials are mixed with a small amount of water and shaped into bricks, followed by microbial cultivation in an incubation room for a week or so, letting the mould grow on the surface of the herbal materials.

3.6.1 Fermentation procedures

- When fermentation is required to produce a herbal preparation, all utensils should be completely cleaned. A non-corrosive fermenter is required.
- The water to be used should comply with local requirement for potable water, not be alkaline and should be free of inorganic matter (deionized water).
- The temperature and length of fermentation should be optimized and controlled.
- When fermentation is complete, the solution should be filtered and stored in suitable containers.

3.7 Advanced cutting and powdering

Cutting and powdering (or grinding) of the crude drug has many advantages as this process facilitates reduction of the plant material to a desirable particle size. During the post-harvest processing stage, primary cutting takes place to reduce the size of large pieces of herb to facilitate transportation and cleaning or washing. In many cases, herbal materials are further cut into small pieces of particular size and shape following traditional practice. In other cases, size reduction of the herbal materials facilitates the process of extraction and the preparation of dosage forms such as capsules. The ground powder is usually subjected to sieve analysis to achieve uniform distribution of a desired particle size. Various types of grinding machines can be utilized depending on the hardness, size, heat stability, friability and structural features of the plant part and output characteristics.

3.7.1 Procedures

The appropriate particle size of a comminuted herbal material depends on its nature and its subsequent processing. When a national pharmacopoeia defines approved size ranges, those standards should be followed. In general, for dried leaves, flowers and whole herbaceous plants, an average particle size of 5–10 mm is adequate for extraction, while for harder materials such as wood, bark, roots, rhizomes and seeds, 0.5–5 mm is recommended. In special cases, such as the extraction of specific alkaloids, 50–500 µm particle size may be desirable. For encapsulation of powders, a particle size of about 1–50 µm is usually required. Very fine powders (for example, nanoparticles) should be avoided for extraction because they have a tendency to block the filters. Nanoparticles may also be used for encapsulation.

Usually particle size reduction is carried out using mills with varying operational functions. Hammer mills are the most commonly used for initial size reduction. They are suitable for pulverizing roots, barks and stems, but not for grinding soft materials such as flowers and leaves. Other types of mills such as crusher mills are good for crushing

fibrous herbal materials, and further size reduction can be achieved by using cutter mills or disc mills.

3.8 Processing documentation

The general principles for documentation are set out in the *Good manufacturing practices for pharmaceutical products: main principles* (5, 8, 17).

In addition to the data called for in the above guidelines, the documentation for herbal preparations should as far as possible include, as a minimum, the following information:

- botanical information as specified in section 2.5;
- batch number, batch size, and any other identification code;
- supplier;
- dates of receipt of the herbal material, processing of the material, and completion of the process;
- name of person in charge of the processing;
- name of quality assurance manager; and person in charge of batch release;
- previous processes that the herbal material has already undergone;
- characteristics of the herbal preparation (such as type of preparation, ratio of the herbal material to the herbal preparation, organoleptic characters);
- methods used for processing to produce herbal preparation;
- details of the procedures (master formula), including quantity of herbal materials, extraction solvent, additive, descriptions of the steps of operation, operational conditions used during the process, and other relevant information;
- weight or amount of the herbal preparation;
- batch production: give details of deviations or modifications of the master formula;
- quality control parameters (such as identification tests, tests on water content and impurities, residual solvents, microbial contamination tests, shelf life), acceptance limits of the tests and quantitative assay results of active ingredients, markers or chemical reference standard(s);
- storage conditions and containers; and
- shelf life and retest period.

An SOP including all processing steps should be adopted and documented in the Master Record. Batch records should be kept and any deviations from the SOP should be fully recorded and investigated. Name(s) of all operators, and the dates and time at which each step or stage are carried out should be documented.

4. Good herbal processing practices for the production of herbal dosage forms

4.1 General information

In contrast to synthetic pharmaceutical preparations, certain herbal materials and herbal preparations may undergo simpler good practice processes to become suitable dosage forms and final products for administration. However, these dosage forms should be produced under applicable GMP (4–6, 8) conditions. Starting materials for the preparation and production of various herbal dosage/final dosage forms should consist of good quality medicinal plants cultivated or collected as prescribed by GACP (1). They should have been subjected to post-harvest processing, followed by further processing into herbal materials or herbal preparations under GHPP as described previously (sections 2 and 3).

Examples of a number of herbal dosage forms are presented in the *Japanese Pharmacopoeia*.⁶

The following describes some common dosage forms of herbal medicines. National and regional regulations and GMP guidelines must be followed for the production of finished products.

4.2 Preparation of liquid herbal dosage forms

Liquid herbal dosage forms as described here are oral preparations, including, but not limited to, the following product types or categories. These liquid herbal dosage forms may be prepared by dissolving the herbal preparation in an aqueous or non-aqueous solvent, by suspending it in an appropriate medium or by incorporating it into one of the two phases of an oil and water system.

4.2.1 Fluidextract

For description, see section 3.2.3.1

4.2.1.1 Preparation of fluidextracts

Fluidextracts are prepared by percolation of herbal material(s) using an aqueous alcoholic menstruum. After being thoroughly moistened, the mixture is packed firmly into a percolator and covered with additional menstruum. It is macerated for 24 hours, then percolated at a moderate rate, adding fresh menstruum as necessary to completion. The first 700–800 mL of the percolate should be reserved for use to dissolve the residue from the additional percolate that has been concentrated to a soft extract at a temperature not

⁶ Ministry of Health, Labour and Welfare, Government of Japan, General Rules for Preparations – [4] Monographs for Preparations Related to Crude Drugs, *Japanese Pharmacopoeia 17th edition*, 2016. <https://www.pmda.go.jp/files/000217650.pdf>.

exceeding 60 °C. The extract is adjusted with menstruum, if necessary, so that it satisfies the requirements for content of solvent (in a ratio of one part (1.0 mL) of liquid to one part (1.0 g) of the herbal material). They may be filtered, if necessary.

4.2.2 Decoctions

For description, see section 3.2.3.1

4.2.2.1 Preparation of decoctions

In many traditional medicine contexts, decoctions are prepared by boiling the herbal materials in water for a certain period of time, after which they are strained and taken directly by the patients. The amounts of water used and the length of boiling are generally specified by the practitioners on a case-by-case basis.

4.2.3 Infusions

For description, see section 3.2.3.1

4.2.3.1 Preparation of infusions

Infusions are prepared by macerating the herbal materials for a short period of time with warm or boiling water.

4.2.4 Tinctures

For description, see section 3.2.3.1

4.2.4.1 Preparation of tinctures

Tinctures are usually prepared by either maceration or percolation, using ethanol, wine or a hydroalcoholic mixture to extract the herbal material, or by dissolving a soft or dry extract of the herbal material in ethanol of the required concentration. Tinctures are adjusted, if necessary, so that they satisfy the requirement for content of solvent (1 part of herbal material and 5–10 parts of solvent). They may be filtered if necessary.

4.2.5 Syrups

Syrups are viscous liquids containing sugars or other sweetening agents. They are prepared by dissolving, mixing, suspending or emulsifying herbal extracts or decoctions in a solution of honey, sucrose or other sweetening agents.

4.2.5.1 Preparation of syrups

Syrups are usually prepared by adding sucrose (at least 45% m/m) to the herbal solution or decoction, and then heating and straining it. Other polyol sweetening agents may be used. Sufficient purified water is then added to yield a product of the desired weight or

volume. Syrups should be made in quantities that can be consumed within a reasonable period of time. If necessary, syrups may contain approved preservatives to prevent bacterial and mould growth.

4.2.6 Oral emulsions

Oral emulsions are preparations consisting of a two-phase system composed of at least two immiscible liquids such as oil-in-water preparations that are rendered homogeneous and stabilized by the addition of emulsifying agent(s). For example, an oil obtained from herbs (for example, castor oil) is dispersed in water and emulsified with an emulsifying agent such as gum acacia.

4.2.6.1 Preparation of oral emulsions

Various techniques can be applied to uniformly disperse one liquid in another immiscible liquid in the form of small droplets throughout the other. When emulsions are prepared, energy must be expended to form an interface between the oily and aqueous phases. Emulsification equipment includes a wide variety of agitators, homogenizers, colloid mills and ultrasonic devices.

4.2.7 Aromatic waters

Aromatic waters are water preparations saturated with essential oils or other aromatic or volatile substances. Aromatic waters have a characteristic odour of the essential oil or volatile substances used.

4.2.7.1 Preparation of aromatic waters

Usually, an essential oil (1 part) is shaken in recently distilled water (999 parts) and set aside for 12 hours or longer after mixing with 10 parts of talcum powder. The solution is filtered and made up to a certain volume with water. Aromatic waters will deteriorate over time due to volatilization, decomposition or mould growth. They should, therefore, be made in small quantities for immediate use and protected from intense light, excessive heat and stored in airtight, light-resistant containers, if necessary.

4.3 Preparation of solid herbal dosage forms

Solid dosage forms as described here are those that are most commonly found in herbal medicine, but they are not limited to the following categories.

4.3.1 Herbal tea bags

Herbal tea bags are used in many traditional medicine systems as a dosage form. Each tea bag contains ground herbal materials (a single herb or a mixture of different herbs) sufficient for one dose for making into an infusion.

4.3.1.1 Preparation of herbal tea bags

Herbal materials (for example, dried roots, leaves or flowers) are put into paper or cloth bags. Herbal tea bags should be free of bleach, gluten and dioxin. Metallic pins, used for attaching a piece of thread to the tea bag, should be avoided as this may release unsafe cations into the solution. When used, boiling water is poured into the vessel or cup containing the bag.

4.3.2 Plant powders

In many traditional medicine systems, ground powders of herbal materials are taken directly by patients as a dosage form. Powders are ground into various coarse or fine particle sizes, excluding nanopowder.

4.3.2.1 Preparation of plant powders

Powders are prepared by grinding or pulverizing dried herbal materials to a suitable particle size. When used, they are suspended in warm water ready for ingestion, or more commonly, they are packed into capsules or sachets.

4.3.3 Dry extract powders (powdered extracts)

Dry extract powders are solid preparations with a powdery consistency, obtained by evaporation of the solvent used for extraction. They may contain suitable added substances such as excipients, stabilizers and preservative, and suitable for incorporation into a dry formulation as in capsules, tablets or granules.

4.3.3.1 Preparation of dry extract powders (powdered extracts)

Dry extract powders are prepared by spray-drying or freeze-drying of a fluid extract with or without the use of an adsorbent (such as methyl cellulose), or by drying and milling to produce a powder. Excipients are often used for purposes such as improving taste or facilitating the packaging step.

4.3.4 Granules

Granules are dried liquid (fluid) extracts processed into spherical particles composed of agglomerations of smaller particles. Typically, granules are reconstituted to a suspension or solution by the addition of water to make a “herbal tea” for administration, although they can be administered directly. They are also used in tablet compression or capsule filling.

4.3.4.1 Preparation of granules

In the typical manufacture of granules, the dried liquid extract is blended with diluents, binders or other suitable excipients, then wetted with an appropriate binding solution

or solvent to promote agglomeration. The composition is dried and sized to yield the desired material properties.

4.3.5 Pills

Pills are dry extract powders in the form of small, spherical solids, similar to, as a rule, but larger than granules (size may vary in different traditional medicine contexts). In certain traditional medicine context, pills are also made from powdered herbs/herbal materials.

4.3.5.1 Preparation of pills

Pills may be prepared by trituration of dried powdered herbs or dry extract powders with suitable powdered excipients in serial dilution to attain a uniform mixture. Liquid excipients that act to bind and provide plasticity are added to the dry materials, and kneaded to form a mass. Typically, pills are swallowed with warm water.

4.3.6 Capsules

Capsules are solid dosage forms in which the herbal substance is enclosed in either a hard or soft, soluble shell of gelatin or other suitable materials. Hard-shell capsules (also known as two-piece capsules) consist of two pieces (a body and a cap) in a range of standard sizes; soft-shell capsules (also known as one-piece or gel capsules) comprise an outer case encapsulating a liquid or paste. The exact composition of the capsule varies with the nature of the content.

4.3.6.1 Preparation of capsules

Capsules are prepared by enclosing a plant powder, or homogeneous dry extract powder or granules with excipients in a suitable capsule base such as gelatin, of a particular shape and size. In the case of gel capsules, liquid extract or soft extract can also be encapsulated. The process is carried out using specialized equipment.

4.3.7 Tablets

Tablets are solid preparations in which the herbal extract powder, plant powder or granule is blended with excipients and formed into a defined shape and size by compression.

4.3.7.1 Preparation of tablets

Tablets are usually prepared by mixing the homogeneous dry extract powder, plant powder or granules with excipients such as diluents and binders, followed by compression into a defined shape and size. Tablets may be coated or uncoated.

4.3.8 Lozenges

Lozenges (compressed lozenges are referred to as “trophes”) are solid dosage forms that are designed to dissolve slowly in the mouth to provide local action in the oral cavity

or the throat, such as cough drops or pastilles, but may also provide systemic action. Lozenges often contain flavouring agents and sweetened bases.

4.3.8.1 Preparation of lozenges

In the typical preparation of lozenges, sucrose (or another excipient such as sorbitol) is cooked with the herbal extract and water. Flavouring and colouring agents are added and thoroughly mixed while cooling. Individual units of the desired shape are formed by filling the molten mass into moulds. Care should be taken to avoid excessive moisture during storage to prevent crystallization of the sugar base.

4.4 Preparation of other herbal dosage forms

4.4.1 Ointments, creams and salves

Ointments, creams and salves are topical preparations for application to the skin. They are usually semi-solid emulsions dissolved or dispersed in a suitable base. Salves are often solid at room temperature. They may contain emulsifiers or thickening agents.

4.4.1.1 Preparation of ointments, creams and salves

Ointments and creams can be formulated with a herbal extract or powder and a variety of oils and emulsifying agents. Preparation usually involves heating, mixing and stirring the lipid and aqueous portions until the mixture has congealed. They usually require the addition of preservative unless they are intended to be used within a relatively short period of time.

4.4.2 Inhalations

Inhalations are preparations intended for administration as aerosols to the bronchial tubes or lungs. They are usually either dry powder inhalers or inhalation liquid preparations. For administration of inhalations, suitable devices or apparatus are required. Steam inhalation of volatile substances from herbal teas or essential oils is used as a traditional inhalation method. The preparations are also used at room temperature with suitable evaporating devices and as sticks when the volatile substance is incorporated in a suitable vehicle.

4.4.2.1 Preparation of inhalations

Dry powder inhalers are prepared by pulverizing dry extracts into fine particles. When necessary, lactose or other suitable excipients are added to make a homogeneous mixture. Inhalation liquid preparations are usually prepared by mixing dry herbal extracts with a vehicle and suitable pH-adjusting agents to make a solution or suspension. Suitable preservatives may be added to prevent the growth of microorganisms.

4.4.3 Plasters and patches

Plasters and patches contain herbal preparations such as dry or soft extracts on pieces of fabric or plastic elastomer sheets in such a way as to adhere to the skin and attach to the backing. When applied topically to the skin, they deliver the active ingredients through the skin to underlying tissues, usually for the relief of pain, backache or sore muscles.

4.4.3.1 Preparation of plasters and patches

A dry or soft extract of herbal preparation is spread uniformly on an appropriate support that is usually made of a rubber base of synthetic resin. Plasters are available in a range of sizes or cut to size to effectively provide prolonged contact with the site of application. They adhere firmly to the skin but can be peeled off without causing injury.

4.4.4 Medicated oils

Medicated oils are preparations formulated using fixed oils as base/vehicle where the prescribed herbal material, extract or fresh juice is mixed, macerated or boiled in oil. Different traditional methods are followed in the preparation of medicated oils but the aim is to obtain an oil enriched with fat-soluble extractives of the desired ingredients.

Medicated oils are mainly used topically, for example, in therapeutic massages and in certain cases, for oral administration.

4.4.4.1 Preparation of medicated oils

A fine paste of powdered herb or herbal material(s) together with a given media (if any, such as water, milk or fresh juices or decoctions of herbal materials) is mixed in a prescribed quantity of oil and macerated or boiled slowly with continuous stirring until complete removal of water or moisture (as the case may be). The oil is then decanted or strained while warm through muslin cloth and allowed to cool.

5. Technical issues supporting good herbal processing practices

In the formulation of a good practice protocol for herbal processing, a number of supporting technical measures must be considered and adopted. Since the primary objective is to produce quality processed herbal materials, herbal preparations and herbal dosage forms, many of the same technical issues associated with GACP, GMP and quality control (QC) methods are applicable to GHPP.

Therefore, these guidelines have been consulted for applicable good practice for adoption in GHPP. Moreover, the same technical issues relating to the post-harvest processing of cultivated and collected medicinal plant materials were addressed in section 4 of the *WHO guidelines on GACP for medicinal plants* (1). Likewise, the same

technical issues relating to the processing of herbal materials and herbal preparations were described in the WHO guidelines on GMP for herbal medicines (5, 6, 8). Thus, the applicable good practice guidelines have been adopted in whole or in part, or modified as appropriate for the present guidelines.

5.1 Processing facilities

The ideal design and construction of a “post-herbal processing” facility incorporating the most appropriate location, buildings, herbal material handling and processing areas, water supply, effluent and waste disposal, changing facilities and toilets, hand-washing facilities in processing areas, disinfection facilities, lighting, ventilation, dust and storage of waste and unusable materials, have already been fully described in sections 4.1.5 (pages 19–23) of the *WHO guidelines on GACP for medicinal plants* (1). Therefore, they are adopted for the present guidelines and the descriptions are presented in Appendix 3 for easy reference.

Additionally, a facility for processing herbal preparations and herbal dosage forms would most appropriately be constructed following the principle of good manufacturing practice, as described in the *WHO guidelines on good manufacturing practice (GMP) for herbal medicines* (5). The relevant descriptions of such a facility are provided in Appendix 4 for easy reference.

5.2 Packaging and labelling

Processed herbal materials, herbal preparations and herbal dosage forms should be packaged as quickly as possible to preserve their quality. Packaging should prevent deterioration of the herbal medicines and they should be protected against exposure to pest infestations and other sources of contamination. When applicable, the maximal holding time of the unpacked herbal medicines should be established.

Continuous in-process QC measures should be implemented to eliminate substandard materials, contaminants and foreign matter prior to and during the final stages of packaging. Processed herbal materials, herbal preparations and herbal dosage forms should be packaged in clean, dry boxes, sacks, breathable bags or other containers in accordance with the SOP and should comply with national and/or regional regulations of the producer and the end-user countries. Materials used for packaging should be non-polluted, clean, dry and undamaged, and should conform to the quality requirements for the processed herbal materials, herbal preparations or herbal dosage forms concerned. Fragile herbal materials should be packaged in rigid containers. Wherever possible, the packaging used should be agreed upon between the supplier and the buyer.

A label affixed to the packaging should include, but is not limited to, the following:

- accepted scientific name of the herb(s);
- official common name of the herb(s), herbal material(s), herbal

- preparation(s) or herbal dosage form(s);
- brand name of the herbal medicines (herb(s), herbal material(s), herbal preparation(s) or herbal dosage form(s));
 - date of the processing of the processed herb(s), herbal material(s), herbal preparation(s), or herbal dosage form(s) obtained;
 - processing techniques used;
 - names and addresses of the herbal materials or herbal preparations processor, herbal dosage forms (finished herbal products) manufacturer, importer and/or distributor (i.e. the entity responsible for receiving consumer complaints and conducting a recall should the need arise);
 - potency or strength of the active ingredient, if applicable (for example, for an extract the drug extract ratio of herbal material to extract, or the concentration of active or marker substance(s) used for standardization);
 - net amount in the immediate container in terms of weight, measure or unit number;
 - in the case of a finished herbal dosage form, the quantity of each active ingredient or marker per dosage unit;
 - list of excipients;
 - recommended storage conditions;
 - batch number; and
 - expiry date.

The label should also contain information indicating quality approval and compliance with national and/or regional labelling requirements.

Finished herbal product labelling should comply with the national/regional regulation/requirements.

Records should be kept of batch packaging, and should include the product name, place of origin, batch number, weight, assignment number and date. The records should be retained for a period of three years or as required by national and/or regional authorities.

5.3 Storage and transportation

All processed herbal medicines should be properly stored and preserved before use. They must be protected from microbial and insect contamination, as well as rodents and other pests. Every effort should be made to use the type of packaging that provides the best protection against physical damage to the processed materials; and at the same time to keep them away, as far as possible, from exposure to moisture, light, heat, insect and animal attack.

Rejected samples should be kept in a separate designated quarantined area, clearly labelled and with a specified handling period.

Toxic or controlled herbal materials or preparations should be checked, labelled and stored according to the government's regulations.

Storage areas should be of sufficient capacity to allow orderly storage of the various types of processed herbal materials, herbal preparations or herbal dosage forms with proper separation and segregation. In particular, they should be clean, dry, sufficiently lit and maintained within acceptable temperature and humidity limits. They should be controlled, monitored and recorded where appropriate to ensure good storage conditions, and comply with the "first-in and first-out" principle.

Conveyances used for transporting processed herbal medicines from the place of processing to the storage location should be clean and, where appropriate, well ventilated to maintain an appropriate airflow and to prevent condensation.

Pest infestation control in conveyances and in storage areas should be carried out by licensed or trained personnel. Only registered chemical agents authorized by the regulatory authorities of the source country and the countries of intended end-use should be used. All fumigation, fumigation agents and dates of application should be documented. When freezing or saturated steam is used for pest control, the humidity of the stored herbal medicines should be checked after treatment.

5.4 Equipment

All equipment, including tools and utensils used in the herbal processing procedures should be made of materials that do not transmit toxic substances, odour or taste; are non-absorbent; are resistant to corrosion and are capable of withstanding repeated cleaning and disinfection. The use of wood and other materials that cannot be adequately cleaned and disinfected should be avoided, except when their use would clearly not be a source of contamination. The use of metals known to cause corrosion should be avoided.

All equipment and utensils should be designed and constructed so as to prevent hygiene hazards and permit easy and thorough cleaning and disinfection. Where practicable, they should be accessible for visual inspection. Stationary equipment should be installed in such a manner as to permit easy access and thorough cleaning.

Containers for unusable materials or waste should be leak-proof, constructed of metal or other suitable impervious materials, should be easy to clean or be disposable, and should close securely.

All refrigerated spaces should be equipped with temperature measurement and recording devices.

5.5 Quality assurance and quality control

A quality assurance system is essential to ensure that herbal processing practice is consistently executed and controlled. The system for verification of compliance may

differ from country to country. In general, compliance with quality assurance measures should be verified through regular internal oversight personnel (quality assurance manager) and external auditing visits to processing facilities by expert representatives of buyers and other stakeholders, and through inspection by national and/or local regulatory authorities. No processed herbal medicine should be released until its quality complies with or conforms to standard specifications.

5.6 Documentation

The SOPs should be adopted and documented. All methods and procedures used in the herbal processing and the dates on which they are carried out should be documented.

The types of information that should be collected include the items described in sections 2.5 and 3.8. Additionally, documentation on post-processing transportation and storage of processed products should be prepared.

Where applicable, the results of inspection should be documented in an inspection report, which contains copies of all documents, QC analysis reports, and local, national and/or regional regulations, and which are stored in compliance with their requirements.

5.7 Personnel

5.7.1 General

All personnel should receive proper training in post-harvest handling and herbal processing. Furthermore, all personnel required to handle chemical solvents and adjuvants should receive adequate training and possess sufficient knowledge of the appropriate techniques to be employed for their safe handling and proper use. Training records should be signed by the trainer and trainee and documented.

Local, national and/or regional regulations governing labour should be respected in the employment of staff for all phases of herbal processing.

5.7.2 Health, hygiene and sanitation

All personnel involved in the pre-herbal processing and during herbal processing procedures should be properly trained and should perform tasks in compliance with local, national and/or regional regulations on safety, materials handling, sanitation and hygiene.

All personnel should be protected from contact with potentially toxic or allergenic herbs by means of adequate protective clothing, including gloves and masks.

Health status

All new staff should pass a medical examination. No personnel known or suspected to be suffering from or to be a carrier of a disease or illness likely to be transmitted, should be allowed to enter any processing area, and should immediately be reported to the management, and suspended from work as deemed medically appropriate.

Health conditions that should be reported to the management for consideration regarding medical examination and/or possible exclusion from handling of herbal medicines and herbal processing, processed herbal medicines and associated equipment include but are not limited to: jaundice, diarrhoea, vomiting, fever, sore throat with fever, visibly infected lesions (boils and cuts, among other conditions) and discharges from the ear, nose or eye. Any personnel who have cuts or wounds and are permitted to continue working should cover their injuries with suitable waterproof dressings.

Personal hygiene and behaviours

Personnel engaged in herbal processing and who handle processed herbal medicines should be trained to maintain a high degree of personal cleanliness, and, where appropriate, wear suitable protective clothing and gloves, including head/hair covering and footwear.

Personnel should always wash their hands at the start of handling activities, after using the toilet, and after handling herbal processing and herbal medicines, or any contaminated material.

Smoking, drinking and eating should not be permitted in herbal processing areas.

Visitors

Visitors to processing and handling areas should wear appropriate protective clothing and adhere to all of the personal hygiene provisions mentioned above (WHO, 2003a).

6. Other relevant issues

6.1 Ethical and legal considerations

All herbal processing must be carried out in accordance with applicable legal and environmental requirements and with the ethical codes or norms of the community and country in which the activities take place.

6.2 Research, research training and information sharing

Research to understand and gain knowledge on the mechanism and scientific basis of processing procedures, such as traditional or historical methods is needed. It is also necessary to conduct research to find alternative processing procedures to achieve the same therapeutic effect as traditional or historical methods. Additionally, research to determine the chemical conversion process and mechanism involved in the qualitative and quantitative alteration of the biologically active chemical constituents following processing is needed and encouraged.

Technical information resulting from research on processing methods is useful for promoting technical advancement, and should be shared through publication, conferences or otherwise conveyed to interested stakeholders.

As in all technical endeavours, education and research training are essential to preserve technical expertise and to promote innovation in development of new and better techniques and procedures in herbal processing.

Research to develop GHPP for individual herbs or herbal materials and to document each in a monograph is strongly encouraged.

6.3 Adoption of good herbal processing practices

Member States or nations that have not adopted GHPP for herbal medicines are encouraged to establish or adopt such practices as part of quality assurance and control measures, as well as a part of their regulatory requirements for herbal medicines.

6.4 Intellectual property rights and benefits-sharing

Agreements on intellectual property rights and the return of benefits and compensation for the use of source herbal materials or herbal preparations concluded in writing by the sourcing contractor, shall be acknowledged and followed by the processor as appropriate (for example “Aichi Protocol” under the framework of the United Nations Convention on Biodiversity).

6.5 Threatened and endangered species

When obtaining herbs or herbal materials that are protected by national and international laws, such as those listed in national “red” lists, for processing, the processor shall ascertain and obtain appropriate documentation from the sourcing contractor that said materials were acquired only by relevant permission according to national and/or international laws, and that the provisions of the Convention on International Trade in Endangered Species of Wild Fauna and Flora have been complied with.

6.6 Safety management of toxic herbs

Among the herbal medicines (and their source medicinal plants) being used in traditional medicine contexts in different parts of the world, some are known to contain toxic substances that may lead to severe side-effects or even death. In general, these toxic herbal materials and their preparations or dosage forms have narrow therapeutic windows between effective dose and lethal dose. Examples of such toxic/effective therapeutic agents are cardioactive herbal preparations such as *Powdered Digitalis* and *Digitalis Capsules*, which at the proper dosages, are excellent therapeutic cardiotonic agents, but are lethal when an overdose is taken.

In order to safeguard the use of these potentially toxic herbs, special attention and safety management measures are required, for example:

- they must go through proper processing procedures for the purpose of neutralizing the toxicity or reducing the side-effects prior to use.

- They must be used under stringent measures of control and supervision by qualified and/or trained personnel.
- When poisoning and/or accidents related to the use of these toxic herbs occur, proper medical treatment should be given immediately.
- Member States should promote and ensure the safe use of potentially toxic herbs and their preparations.
- Member States are encouraged to establish national policies to achieve effective control of herbal safety and to strengthen risk assessment and management.
- Member States are encouraged to develop their own standards and guidelines for the use of potentially toxic medicinal plants.

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Appendix 1

Example of a model format for a good herbal processing practices monograph/standard operating procedure protocol to produce a herbal material

TITLE of the monograph/protocol

Processing of (name of the plant) (*Scientific name of the medicinal plant; medicinal plant part*)

1. Objective of the standard operating procedure (SOP) protocol

2. Scope

3. Procedures

3.1 Sampling

Sampling of herbal materials should follow applicable national or regional specifications. In absence of appropriate specifications, the following method may be considered: When a batch consists of five containers or packaging units, take a sample from each one. From a batch of 6–50 units, take a sample from five. In the case of batches of over 50 units, sample 10%, rounding up the number of units to the nearest multiple of 10 (WHO, 2011).

Quality testing of the raw material

Perform morphological identification/validation by macroscopic, microscopic or phytochemical and/or genomic identification/examinations and physicochemical tests by following the procedures set out in the national pharmacopoeia or other documents.

The following requirements must be fulfilled.

- Morphology: conform with the national pharmacopoeial or other relevant standards
- Identification (including macroscopic, microscopic examination, phytochemical and/or genomic identification/examinations, and/or chromatographic tests): conform with the pharmacopoeial standards
- Water content: ≤ xxx %
- Total ash: ≤ xxx %

- Acid-insoluble ash: \leq xxx %
- Extractive: \geq xxx %

3.2 Quality control assay

3.2.1 Marker compound(s)

Compound “Z” is used as the marker compound for plant X..y.. for quality control purpose. Obtain analytical grade Compound Z (\geq 98% purity) from a reliable source to serve as chemical reference substance.

3.2.2 High-performance liquid chromatographic analysis

Set up the high-performance liquid chromatography (HPLC) system. Perform system suitability test to ensure suitability of the instrument and method.

Under the recommended HPLC conditions, establish calibration curves by injecting an appropriate amount of the chemical reference (marker) standard solution in a series of concentrations.

Obtain HPLC chromatogram of the herbal material. Identify the analyte signal in the chromatogram by comparing the retention time with that of the peak of the chemical reference substance obtained under same HPLC conditions.

Calculate the percentage content of the analyte in the sample using the calibration curve.

Determine the percentage content of the marker compound again after final drying of the processed herbal material (section 3.10 below).

The following requirement must be fulfilled.

- Content of Compound Z before processing: \geq xxx % calculated with reference to the dry weight of the starting material
- Content of Compound Z after processing: \geq xxx % calculated with reference to the dry weight of the processed material

3.3 Testing of the excipient*

(*This step is not required if excipient(s) are not employed in the processing protocol)

Perform tests by following the procedures set out in the SOP document. The following requirements must be fulfilled.

- Appearance: conform with internal standards
- Total excipient content: \geq xxx %

3.4 Initial sorting of herb for processing

The source herbs are manually sorted by trained personnel according to the requirements specified in the SOP. Impurities (for example, dirt and non-medicinal plant parts) should be removed, and any materials of non-uniformed sizes should be excluded.

The following requirements must be fulfilled.

- Impurity: \leq xxx %
- Size uniformity: \geq xxx %
- Total recovery: \geq xxx % (Recovery = Weight after sorting/Weight before sorting X 100%)

3.5 Washing

Washing should be performed by following the procedures set out in the SOP document. Pay attention to the quality of water used, the length of washing time, and any precautions applicable to the specific herb.

The following requirements must be fulfilled.

- Appearance after washing: in conformance with the SOP standard
- Recovery: xxx-xxx % (Recovery = Weight after washing/Weight before washing X 100%)

3.6 Steaming (or other treatment)

The procedures set out in the SOP document should be strictly followed. All equipment should be properly maintained, clean and performing at optimal and safe conditions.

The following requirements must be fulfilled.

- Appearance after steaming/treatment: in conformance with the SOP standard
- Recovery: \geq xxx % (Recovery = Weight after steaming/Weight before steaming X 100%)

3.7 Semi-drying

If required, dry the samples according to SOP guidelines, either by sunlight or by artificial heating.

The following requirements must be fulfilled.

- Appearance after semi-drying : in conformance with the SOP standard
- Recovery: xxx-xxx% (Recovery = Weight after drying/Weight before drying \times 100%)

3.8 Cutting/sectioning/comminuting

The processed material should be comminuted into the required size and shape in conformance with the SOP.

The following requirements must be fulfilled.

- Non-conforming pieces: \leq xxx %
- Powder fineness:
- Recovery: \geq xxx % (Recovery = Weight after cutting/Weight before cutting \times 100%)

3.9 Final drying of processed herbal material

The cut materials should be thoroughly dried according to the SOP requirement.

The following requirements must be fulfilled.

- Water content of the final product: xxx-xxx %
- Recovery: \geq xxx % (Recovery = Weight after drying/Weight before drying \times 100%)

3.10 Final sorting

The dried material should be carefully inspected by trained personnel, with impurities removed and sorted into specific grades in accordance with the pharmacopoeial or trading standard.

The following requirements must be fulfilled.

Impurity: \leq xxx %

Grade-1 pieces: \geq xxx%

Grade-2 pieces: xxx -xxx%

Recovery: \geq xxx % (Recovery = Weight after sorting/Weight before sorting \times 100%)

3.11 Packaging, labelling and storage

3.11.1 Packaging

Processed materials should be packaged quickly and appropriately in appropriate, non-corrosive containers, and protected from light to preserve quality, prevent deterioration and to protect against contamination.

3.11.2 Labelling

Labels affixed to each package should clearly indicate the scientific name of the medicinal plant, the plant part, the processing method, the date of processing, the batch number, quality specification and compliance, quantitative and other relevant information, in compliance with the national/regional requirements.

3.11.3 Storage

The packaged products must be stored in a clean, dry and well-ventilated area, at a temperature appropriate for the proper maintenance of the final product, and protected against microbial and other sources of contamination and free from insects and animal pest attacks.

Appendix 2

Example of a model format for a good herbal processing practices monograph/standard operating procedure protocol to produce a herbal preparation or herbal dosage form

TITLE of the monograph/protocol

Processing of (name of the plant) (*Scientific name of the medicinal plant; medicinal plant part*)

1. Objective of the standard operating procedure protocol

The objective of this protocol is to establish a procedure for preparation of the finished product.

2. Scope

This procedure applies to processes required in the preparation of the fluidextract of the herbal material from X...y...

3. Procedures

This protocol should be carried out in accordance with the standard operating procedures (SOP) for the processing of material X...y... as described in this document, the SOP for equipment operation and maintenance, as well as those for facility management and cleaning. Any other relevant requirements may also apply.

The protocol should be adhered to in conjunction with relevant internal standards of the processing facility.

After the completion of each processing step, the products should be inspected by qualified personnel. All inspection records should be properly filed and retained for a period of three years or as required by national and/or regional authorities.

4. Herbal material

The identity of the herbal material should be confirmed using morphological identification/validation by macroscopic and microscopic examinations, as well as by using phytochemical and/or genomic identification/examinations, and physicochemical tests by following the procedures set out in the pharmacopoeia or other documents.

Specifications such as those below should be in place.

- **Origins of the herb (natural state/cultivation):** Describe appropriate origins of the herbal material
- **Plant part:** Describe the desired plant part (i.e. flower)
- **Harvest/collection time:** Describe the appropriate months for harvest/ collection (for example during flowering (June-July))
- **Processing:** Describe the processing of the herbal material
- **Drying conditions:** Describe the process for drying, if applicable
- **Purification:** Describe the process for inspection and removal of impurities
- **Storage conditions:** Specify the storage conditions. In general, the herbal material should be stored in a clean, dry and well-ventilated area, at a constant, appropriate temperature, protected against microbial and other sources of contaminations, free from attack by insects and animal pests
- **Transportation conditions:** Commercial vehicles should be clean, dry, deprived of any foreign matter. Conditions should ensure protection against moisture and contamination. Baskets, chests and jute bags can be used as containers. Each container should be labelled with the name of the material, date of harvest/collection, harvesting/collection site, net and gross weight and the name of the supplier

5. Processing

Descriptions of the herbal processing facility requirements should be maintained, i.e. certification of the site as a good practice facility. Details are given here for the raw components to be used in the production of the final herbal preparation.

As an example, raw X...y... herbal material to be processed into X...y... juice are detailed in the table below. In this example, the herbal material is extracted using ethanol 95% (V/V) and water as needed. The drug extract ratio is 1:1.

Raw material components in the production of X...y...juice

Raw materials	Function	Amount per 100 kg	Standard
Fresh X...y... herb	Herbal material	100.0 kg	Standard specification
Ethanol 95%	Extraction solvent	xx litres	Pharmacopoeia .XYZ
Extraction water	Extraction solvent	<i>quantum satis</i>	Pharmacopoeia .XYZ

Raw materials accepted for processing must meet specifications for identity and quality. Specifications include appearance/description of the herbal material, water content, total ash, as well as appropriate chemical assays. These criteria may follow criteria detailed in pharmacopoeial monograph(s).

- The steps below describe the preparation of the juice of X.y.:
 - Step 1. The fresh fragmented herbal material is stabilized with the vapours of boiling 95% ethanol in an autoclave. The duration, temperature and vapour pressure are specified in the SOP. When the process is completed, the fluid separates from the herbal material.
 - Step 2. The stabilized herbal material is placed in a macerator with post-stabilization fluid and water. The maceration process lasts for a period of time (n days) specified. At the end of the extraction process, the extract is separated from the solid materials in a manner specified by the SOP. The ethanol content of the extract and density of the extract are specified.
 - Step 3. The resulting extract is stored in a stainless steel container for a minimum time (days/weeks) specified. The process ensures sedimentation of inorganic residual waste.
 - Step 4. The extract is filtered using a pressurized process. The filter size and input pressure are selected as specified by the manufacturer or manufacturer's catalogue of the filtering unit.

6. In-process controls

Controls for tests conducted during the process should be described. A description of the tests, their methods and the acceptance criteria should be given. These include appearance (i.e. colour), particle size (amount expected to pass through a specified sieve size), water or alcohol content, and/or relative density.

7. Herbal dosage form

The herbal dosage forms may include extracts, pills, spirits, infusions, decoctions, teabags, tinctures, aromatic waters and fluidextracts (see footnote¹).

8. Release specifications of final product

Identify criteria must be met for release of the final product. These criteria generally include appearance, organoleptic characteristics, relative density, chemical identity including specified quantities for chemical constituent(s), as well as limits for heavy metals, microbial contamination and residual matter.

- Chemical profile: i.e. TLC/HPLC fingerprint of chemical constituents
- Pharmacopoeial/standard quantitation of chemical markers, where applicable

¹ A herbal preparation or a specific dosage form, as indicated above, can be prepared as per established pharmacopoeial methods.

- Heavy metals: limits defined
- Microbial: limits defined
- Residuals: limits for pesticides, fertilizers, foreign matter, solvent residue, mycotoxins, etc.

9. Certificate of analysis

A certificate of analysis should be generated following completion of quality control testing. This document should include the assay methods as well as the results obtained using those methods.

10. Packaging

The appropriate packaging of the containers should be described. Processed materials should be packaged quickly and appropriately in airtight, non-corrosive containers, and protected from light to preserve quality, prevent deterioration and to protect against contamination.

11. Labelling

Labels affixed to each package should clearly indicate the scientific name of the medicinal plant, the plant part, the herbal processing method, the date of processing, the batch number, quality specification and compliance, quantitative and other relevant information, in compliance with the national/regional requirements.

12. Storage conditions

The packaged products must be stored in a clean, dry and well-ventilated area, at a temperature appropriate for the proper maintenance of the final product, and protected against microbial and other sources of contaminations and free from insects and animal pest attacks.

13. Stability

Stability testing should be conducted to determine an appropriate shelf life.

14. Retained samples

Sufficient materials (raw material and finished goods) must be retained in proper storage conditions to allow for future verification of identity and quality.

Appendix 3

Processing facilities for post-harvest processing

The following is extracted from section 4.1.5 of the *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants* (WHO, 2003) (pages 19–23).

Processing facilities

In constructing or designing a processing facility, the following elements should be considered that will allow the establishment of a quality assurance system adaptable to the different types and steps of processing to yield the desired end-products.

Location

Facilities should preferably be located in areas that are free from objectionable odours, smoke, dust or other contaminants and are not subject to flooding or other natural adverse conditions.

Buildings

Buildings should be of sound construction and maintained in good repair. Filthy areas must be isolated from clean processing areas. All construction materials should be such that they do not transmit any undesirable substance including toxic vapours to medicinal plant materials. Electrical supply, lighting and ventilation should be appropriately installed.

Buildings should be designed to:

- provide adequate working space and storage room to allow for satisfactory performance of all operations;
- facilitate efficient and hygienic operations by allowing a regulated flow in processing from the arrival of the raw medicinal plant materials at the premises to the dispatch of the processed medicinal plant materials;
- permit appropriate control of temperature and humidity;
- permit control of access to different sections, where appropriate;
- permit easy and adequate cleaning and facilitate proper supervision of hygiene;
- prevent the entry of environmental contaminants such as smoke, dust, the entrance and harbouring of pests, livestock and domesticated animals;
- where appropriate, prevent direct sunlight from entering a particular section.

Medicinal plant material handling and processing areas

The layout and design of the work area should be such as to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, and otherwise avoid any adverse effect on the quality of the processed product.

- Windows and other openings should be constructed so as to avoid accumulation of dirt, and where appropriate, those that open should be fitted with insect-proof screens. Screens should be easily removable for cleaning and kept in good repair. Internal window sills, if present, should be sloped to prevent use as shelves.
- Doors should have smooth, non-absorbent surfaces and, where appropriate, be self-closing and close-fitting.
- Overhead structures and fittings should be installed in such a manner as to avoid contamination of medicinal plant materials (both raw and processed) by condensation and drippings, and should be protected to prevent contamination in case of breakage. They should be insulated, where appropriate and be designed and finished so as to prevent the accumulation of dirt and to minimize condensation, mould development and flaking. They should be easy to clean.
- Food preparation and eating areas, changing facilities, toilets should be completely separated from and not open directly onto medicinal plant material processing areas.

Water supply

- An ample supply of potable water, under adequate pressure and at suitable temperature, used for processing medicinal plant materials, should be available with appropriate facilities for its storage, where necessary, and distribution with proper protection against contamination.
- Ice should be made from potable water; it should be manufactured, handled and stored so as to protect it against contamination.
- Unless there is a post-water filtration or treatment system, non-potable water used for steam production, refrigeration, fire control and other similar purposes not connected with processing should be carried in completely separate pipes, identifiable preferably by colour and with no cross-connection with or back siphonage into the system carrying potable water.

Effluent and waste disposal

Facilities should have an effective effluent and waste disposal system, which should at all times be maintained in good order and repair; and should be constructed so as to avoid contamination of potable water supplies.

Changing facilities and toilets

Adequate, suitable and conveniently located changing facilities and toilets should be provided. Hand-washing facilities with warm or hot and cold water, a suitable hand-cleaning preparation and hygienic means of drying should be provided adjacent to toilets and located so that employees have to pass them when returning to the processing area. Notices should be posted directing personnel to wash their hands after using the toilet.

Hand-washing facilities in processing areas

Adequate and conveniently located facilities for hand-washing and a hygienic means of drying should be provided whenever the process demands. Where appropriate, facilities for hand disinfection should also be provided.

Disinfection facilities

Where appropriate, adequate facilities for cleaning and disinfection of working implements and equipment should be provided. These facilities should be constructed of corrosion-resistant materials, should be easy to clean, and should be fitted with hot and cold water supplies.

Lighting

Adequate natural or artificial lighting should be fitted throughout the facility. Where appropriate, the lighting should not alter colours of the medicinal plants undergoing processing.

Ventilation

Adequate ventilation should be provided to prevent excessive heat, steam condensation and dust and to remove contaminated air from both the processing and storage areas/facilities.

Storage of waste and unusable materials

Facilities should be provided for the storage of waste and unusable materials prior to removal from the premises.

Appendix 4

Processing facilities for production of herbal preparations and herbal dosage forms

The following is extracted from section 12 of the WHO guidelines on good manufacturing practices (GMP) for herbal medicines (WHO, 2007a) (pages 41–44).

Premises

In principle, the premises must be located, designed, constructed, adapted and maintained for the suitable processing/production operations to be performed.

General

In general, the layout and design of the facility must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of the end-products.

- Where dust is generated (for example, during sampling, weighing, mixing and process operations, packaging of powders), measures should be taken to avoid cross-contamination and facilitate cleaning.
- The facility should be situated in an environment that, when considered together with measures to protect the processing/manufacturing process, presents minimum risk of causing any contamination of materials or products.
- The facility should be situated in an environment that, when considered together with measures to protect the processing/manufacturing process, presents minimum risk of causing any contamination of materials or products.
- The facility used for the processing of herbal preparations or manufacture of finished products should be suitability designed and constructed to facilitate good sanitation.
- It should be carefully maintained, and be ensured that repair and maintenance operations do not present any hazard to the quality of products.
- It should be cleaned and, where applicable, disinfected according to written procedures, and records maintained.
- Electrical supply lighting, temperature, humidity and ventilation should be appropriate so that they do not adversely affect, directly or indirectly, the herbal products during their processing/manufacturing and storage, or the functioning equipment.

- It should be designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals.
- It should be designed to ensure the logical flow of materials and personnel.

Ancillary areas

- Rest and refreshment rooms should be separated from processing/manufacturing and control areas.
- Facilities for changing and storage of clothes, for toilet and washing purposes should be accessible for users.
- Maintenance workshops should be separated, if possible, from production areas or tools kept in rooms or lockers.
- Animal houses should be well isolated from other areas, with separate entrance and air handling facilities.

Storage areas

- Storage areas should be of sufficient capacity to allow orderly storage of various categories of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished/processed products, products in quarantined and released, rejected, returned or recalled.
- Storage areas should be designed or adapted to ensure good storage conditions. They should be clean, dry, sufficiently lit and maintained within acceptable temperature limits. Where special conditions (for example, temperature and humidity) are required, they should be provided.
- Receiving and dispatch areas should be separated and protect materials and products from weather; and should be designed and equipped to allow containers to be cleaned if necessary.
- Where quarantine status is ensured by storage in separate areas, they must be clearly marked and access restricted to authorized personnel.
- Segregation should be provided for the storage of rejected, recalled or returned materials or products.
- Highly active and radioactive materials, narcotic and other dangerous materials presenting special risks, fire or explosion, should be stored in safe and secure areas.
- Printed packaging materials are considered critical to the conformity of the processed material/product to its labelling, and special attention should be paid to sampling and the safe and secure storage of these materials.
- There should be a separate sampling area for starting materials.

Weighing areas

- The weighing of starting materials and the estimation of yield by weighing should be carried out in separate areas designed for that use.

Production areas

- In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the processing or manufacture of particular herbal preparations/products, such as toxic and/or rare materials/products.
- Premises should be laid out as to allow the production to take place in such a way as to allow the processing/production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
- The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different herbal preparations/products or their components, to avoid cross-contamination and to minimize the risk of omission or wrong application of any manufacturing or control steps.
- Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces of the facility should be smooth and free from cracks and open joints.
- Pipe work, light fittings ventilation points, and other services should be designed and sited to avoid the creation of recesses that are difficult to clean.
- Drains should be of adequate size and designed and equipped to prevent back-flow.
- Production areas should be effectively ventilated, with air control facilities appropriate to the herbal material/product handled, to the operations taken and to the environment. These areas should be regularly monitored during both processing/production and non-production/non-production periods to ensure compliance with their designed specifications.
- Premises for the packaging of processed/finished products should be specifically designed and laid out so as to avoid mix-ups or cross-contaminations.
- Production areas should be well lit, particularly where visual on-line controls are carried out.

Quality control areas

- Quality control laboratories should be separated from production areas.
- Quality control laboratories should be designed to suit the operations to be carried out in them. Sufficient spaces should be given to avoid mix-ups and cross-contaminations. There should be adequately suitable storage space for samples, reference standards (in appropriate storage facility), solvents, reagents and records.
- The design of the laboratories should take into consideration the suitability of construction materials, prevention of fumes and ventilation. There should be separate air supply to laboratories and processing/production areas.
- Instruments should be housed in a separate room to protect them against electrical interference, vibration, contact with moisture and other external factors, or where it is necessary to isolate the instruments.

5. Laboratory guidelines

5.1 WHO good practices for pharmaceutical quality control laboratories

Annex 1, WHO Technical Report Series, 957,
2010 (under revision)

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General considerations

The WHO Expert Committee on Specifications for Pharmaceutical Products adopted in 1999 the guidelines entitled *WHO Good practices for national pharmaceutical control laboratories*, which were published as Annex 3 of the WHO Technical Report Series, No. 902, 2002. As the other guidelines related to laboratory quality assurance have been updated and subsequent inspections for the compliance with the guidelines on good practices for national pharmaceutical control laboratories indicated that some sections were in need of improvement and clarification, it was considered necessary to prepare a revised text.

These guidelines provide advice on the quality management system within which the analysis of active pharmaceutical ingredients (APIs), excipients and pharmaceutical products should be performed to demonstrate that reliable results are obtained.

Compliance with the recommendations provided in these guidelines will help promote international harmonization of laboratory practices and will facilitate cooperation among laboratories and mutual recognition of results.

Special attention should be given to ensure the correct and efficient functioning of the laboratory. Planning and future budgets should ensure that the necessary resources are available *inter alia* for the maintenance of the laboratory, as well as for an appropriate infrastructure and energy supply. Means and procedures should be in place (in case of possible supply problems) to ensure that the laboratory can continue its activities.

These guidelines are applicable to any pharmaceutical quality control laboratory, be it national, commercial or nongovernmental. However, they do not include guidance for those laboratories involved in the testing of biological products, e.g. vaccines and blood products. Separate guidance for such laboratories is available.

These guidelines are consistent with the requirements of the *WHO guidelines for good manufacturing practices* (1) and with the requirements of the International Standard ISO/IEC 17025:2005 (2), and provide detailed guidance for laboratories performing quality control of medicines. The guidance specific to microbiology laboratories can be found in the draft working document *WHO guideline on good practices for pharmaceutical microbiology laboratories* (reference QAS/09.297).

The good practice outlined below is to be considered as a general guide and it may be adapted to meet individual needs provided that an equivalent level of quality assurance is achieved. The notes given provide clarification of the text or examples; they do not contain requirements which should be fulfilled to comply with these guidelines.

Pharmaceutical quality control testing is usually a matter of repetitive testing of samples of APIs or of a limited number of pharmaceutical products, whereas national quality control laboratories have to be able to deal with a much wider range of pharmaceutical substances and products and, therefore, have to apply a wider variety of test methods. Specific recommendations for national pharmaceutical quality control

laboratories are addressed in the following text. Particular consideration is given to countries with limited resources wishing to establish a governmental pharmaceutical quality control laboratory, having recently done so, or which are planning to modernize an existing laboratory.

Quality control laboratories may perform some or all quality control activities, e.g. sampling, testing of APIs, excipients, packaging materials and/ or pharmaceutical products, stability testing, testing against specifications and investigative testing.

For the quality of a medicine sample to be correctly assessed:

- The submission of a sample of an API, excipient or pharmaceutical product or a suspected counterfeit material to the laboratory, selected in accordance with national requirements, should be accompanied by a statement of the reason why the analysis has been requested.
- The analysis should be correctly planned and meticulously executed.
- The results should be competently evaluated to determine whether the sample complies with the specifications or other relevant criteria.

National pharmaceutical quality control laboratories

The government, normally through the national medicines regulatory authority (NMRA), may establish and maintain a pharmaceutical quality control laboratory to carry out the required tests and assays to verify that APIs, excipients and pharmaceutical products meet the prescribed specifications. Large countries may require several pharmaceutical quality control laboratories which conform to national legislation, and appropriate arrangements should, therefore, be in place to monitor their compliance with a quality management system. Throughout the process of marketing authorization and post marketing surveillance, the laboratory or laboratories work closely with the NMRA.

A national pharmaceutical quality control laboratory provides effective support for an NMRA acting together with its inspection services. The analytical results obtained should accurately describe the properties of the samples assessed, permitting correct conclusions to be drawn about the quality of the samples of medicines analysed, and also serving as an adequate basis for any subsequent administrative regulations and legal action.

National pharmaceutical quality control laboratories usually encompass essentially two types of activity:

- compliance testing of APIs, pharmaceutical excipients and pharmaceutical products employing “official” methods including pharmacopoeial methods, validated analytical procedures provided by the manufacturer and approved by the relevant government authority for marketing authorization or validated analytical procedures developed by the laboratory; and

- investigative testing of suspicious, illegal, counterfeit substances or products, submitted for examination by medicine inspectors, customs or police.

To ensure patient safety, the role of the national pharmaceutical quality control laboratory should be defined in the general pharmaceutical legislation of the country in such a way that the results provided by it can, if necessary, lead to enforcement of the law and legal action.

Glossary

The definitions given below apply to the terms as used in these guidelines. They may have different meanings in other contexts.

acceptance criterion for an analytical result

Predefined and documented indicators by which a result is considered to be within the limit(s) or to exceed the limit(s) indicated in the specification.

accuracy

The degree of agreement of test results with the true value or the closeness of the results obtained by the procedure to the true value (1).

Note: It is normally established on samples of the material to be examined that have been prepared to quantitative accuracy. Accuracy should be established across the specified range of the analytical procedure. It is generally acceptable to use a “spiked” placebo which contains a known quantity or concentration of a reference substance.

active pharmaceutical ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body (1).

analytical test report

An analytical test report usually includes a description of the test procedure(s) employed, results of the analysis, discussion and conclusions and/or recommendations for one or more samples submitted for testing (see Part three, sections 18.7–18.11).

analytical worksheet

A printed form, an analytical workbook or electronic means (e-records) for recording information about the sample, as well as reagents and solvents used, test procedure applied, calculations made, results and any other relevant information or comments (see Part three, section 15).

batch (or lot)

A defined quantity of starting material, packaging material or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches which are later brought together to form a final homogeneous batch. In the case of terminal sterilization the batch size is determined by the capacity of the autoclave. In continuous manufacture the batch should correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval (1).

batch number (or lot number)

A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis (1).

calibration

The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established (1).

certificate of analysis

The list of test procedures applied to a particular sample with the results obtained and the acceptance criteria applied. It indicates whether or not the sample complies with the specification (3).

certified reference material

Reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, its associated uncertainty and a statement of metrological traceability (4).

compliance testing

Analysis of active pharmaceutical ingredients (APIs), pharmaceutical excipients, packaging material or pharmaceutical products according to the requirements of a pharmacopoeial monograph or a specification in an approved marketing authorization.

control sample

A sample used for testing the continued accuracy and precision of the procedure. It should have a matrix similar to that of the samples to be analysed. It has an assigned value with its associated uncertainty.

design qualification (DQ)

Documented collection of activities that define the functional and operational specifications of the instrument and criteria for selection of the vendor, based on the intended purpose of the instrument.

Note: Selection and purchase of a new instrument should follow a conscious decision process, based on the needs of the technical management. When designing a new laboratory facility, the design specification and the requirements for services should be agreed between the management team and the agreed suppliers and documented.

good manufacturing practice(s) (GMP)

That part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization (1).

installation qualification (IQ)

The performance of tests to ensure that the analytical equipment used in a laboratory is correctly installed and operates in accordance with established specifications.

management review

A formal, documented review of the key performance indicators of a quality management system performed by top management.

manufacturer

A company that carries out operations such as production, packaging, testing, repackaging, labelling and/or relabelling of pharmaceuticals (1).

marketing authorization (product licence, registration certificate)

A legal document issued by the competent medicines regulatory authority that authorizes the marketing or free distribution of a pharmaceutical product in the respective country after evaluation for safety, efficacy and quality. In terms of quality it establishes inter alia the detailed composition and formulation of the pharmaceutical product and the quality requirements for the product and its ingredients. It also includes details of packaging, labelling, storage conditions, shelf-life and approved conditions of use.

measurement uncertainty

Non-negative parameter characterizing the dispersion of quantity values being attributed to a measurand (analyte), based on the information used (4).

metrological traceability

Property of a measurement result whereby the result can be related to a reference through a documented, unbroken chain of calibrations, each contributing to the measurement uncertainty (4).

operational qualification (OQ)

Documented verification that the analytical equipment performs as intended over all anticipated operating ranges.

out-of-specification (OOS) result

All test results that fall outside the specifications or acceptance criteria established in product dossiers, drug master files, pharmacopoeias or by the manufacturer (5).

performance qualification (PQ)

Documented verification that the analytical equipment operates consistently and gives reproducibility within the defined specifications and parameters for prolonged periods.

pharmaceutical excipient

A substance, other than the active pharmaceutical ingredient (API), which has been appropriately evaluated for safety and is included in a medicines delivery system to:

- aid in the processing of the medicines delivery system during its manufacture;
- protect, support or enhance stability, bioavailability or patient acceptability;
- assist in pharmaceutical product identification; or
- enhance any other attribute of the overall safety and effectiveness of the medicine during its storage or use (6, 7).

pharmaceutical product

Any material or product intended for human or veterinary use, presented in its finished dosage form or as a starting material for use in such a dosage form, which is subject to control by pharmaceutical legislation in the exporting state and/or the importing state (1).

precision

The degree of agreement among individual results when the procedure is applied repeatedly to multiple samplings of a homogeneous sample. Precision, usually expressed as relative standard deviation, may be considered at three levels: repeatability (precision under the same operating conditions over a short period of time), intermediate precision (within laboratory variations — different days, different analysts or different equipment) and reproducibility (precision between laboratories).

primary reference substance (or standard)

A substance that is widely acknowledged to possess the appropriate qualities within a specified context, and whose assigned content is accepted without requiring comparison with another chemical substance (8).

Note: Pharmacopoeial chemical reference substances are considered to be primary reference substances. In the absence of a pharmacopoeial reference substance, a manufacturer should establish a primary reference substance.

qualification of equipment

Action of proving and documenting that any analytical equipment complies with the required specifications and performs suitably for its intended purpose (see Part two, section 12).

quality control

All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics.

quality management system

An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality (see Part one, section 2).

quality manager

A member of staff who has a defined responsibility and authority for ensuring that the management system related to quality is implemented and followed at all times (see Part one, section 1.3(j)).

quality manual

A handbook that describes the various elements of the quality management system for assuring the quality of the test results generated by a laboratory (see Part one, sections 2.1–2.2).

quality unit(s)

An organizational unit, independent of production, which fulfils both quality assurance and quality control responsibilities. This can be in the form of separate quality assurance and quality control or a single individual or group, depending on the size and structure of the organization.

reference material

Material sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process (4).

reference substance (or standard)

An authenticated, uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use (8).

secondary reference substance (or standard)

A substance whose characteristics are assigned and/or calibrated by comparison with a primary reference substance. The extent of characterization and testing of a secondary reference substance may be less than for a primary reference substance (8).

Note: Often referred to as an “in-house” working standard.

signature (signed)

Record of the individual who performed a particular action or review. The record can be initials, full handwritten signature, personal seal or authenticated and secure electronic signature.

specification

A list of detailed requirements (acceptance criteria for the prescribed test procedures) with which the substance or pharmaceutical product has to conform to ensure suitable quality.

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations both general and specific.

standard uncertainty

Uncertainty of the result of a measurement expressed as a standard deviation (4, 9, 10).

system suitability test

A test which is performed to ensure that the analytical procedure fulfils the acceptance criteria which had been established during the validation of the procedure. This test is performed before starting the analytical procedure and is to be repeated regularly, as appropriate, throughout the analytical run to ensure that the system’s performance is acceptable at the time of the test.

validation of an analytical procedure

The documented process by which an analytical procedure (or method) is demonstrated to be suitable for its intended use.

verification of an analytical procedure

Process by which a pharmacopoeial method or validated analytical procedure is demonstrated to be suitable for the analysis to be performed.

verification of performance

Test procedure regularly applied to a system (e.g. liquid chromatographic system) to demonstrate consistency of response.

Part One. Management and infrastructure

1. Organization and management

- 1.1 The laboratory, or the organization of which it is part, should be an entity that is legally authorized to function and can be held legally responsible.
- 1.2 The laboratory should be organized and operate so as to meet the requirements laid down in these guidelines.
- 1.3 The laboratory should:
 - (a) have managerial and technical personnel with the authority and resources needed to carry out their duties and to identify the occurrence of departures from the quality management system or the procedures for performing tests and/or calibrations, validation and verification, and to initiate actions to prevent or minimize such departures;
 - (b) have arrangements to ensure that its management and personnel are not subject to commercial, political, financial and other pressures or conflicts of interest that may adversely affect the quality of their work;
 - (c) have a policy and procedure in place to ensure confidentiality of
 - information contained in marketing authorizations,
 - transfer of results or reports,
 - and to protect data in archives (paper and electronic);
 - (d) define, with the aid of organizational charts, the organization and management structure of the laboratory, its place in any parent organization (such as the ministry or the NMRA in the case of a national pharmaceutical quality control laboratory), and the relationships between management, technical operations, support services and the quality management system;
 - (e) specify the responsibility, authority and interrelationships of all personnel who manage, perform or verify work which affects the quality of the tests and/or calibrations, validations and verifications;
 - (f) ensure the precise allocation of responsibilities, particularly in the designation of specific units for particular types of medicines;

- (g) nominate trained substitutes/deputies for key management and specialized scientific personnel;
- (h) provide adequate supervision of staff, including trainees, by persons familiar with the test and/or calibration, validation and verification methods and procedures, as well as their purpose and the assessment of the results;
- (i) have management which has overall responsibility for the technical operations and the provision of resources needed to ensure the required quality of laboratory operations;
- (j) designate a member of staff as quality manager who, irrespective of other duties he/she may have, will ensure compliance with the quality management system. The nominated quality manager should have direct access to the highest level of management at which decisions are taken on laboratory policies or resources;
- (k) ensure adequate information flow between staff at all levels. Staff are to be made aware of the relevance and importance of their activities;
- (l) ensure the traceability of the sample from receipt, throughout the stages of testing, to the completion of the analytical test report;
- (m) maintain an up-to-date collection of all specifications and related documents (paper or electronic) used in the laboratory; and
- (n) have appropriate safety procedures (see Part four).

1.4 The laboratory should maintain a registry with the following functions:

- (a) receiving, distributing and supervising the consignment of the samples to the specific units; and
- (b) keeping records on all incoming samples and accompanying documents.

1.5 In a large laboratory, it is necessary to guarantee communication and coordination between the staff involved in the testing of the same sample in different units.

2. Quality management system

2.1 The laboratory or organization management should establish, implement and maintain a quality management system appropriate to the scope of its activities, including the type, range and volume of testing and/or calibration, validation and verification activities it undertakes. The laboratory management should ensure that its policies, systems, programmes, procedures and instructions are described to the extent necessary to enable the laboratory to assure the quality of the test results that it generates. The documentation used in this quality management

system should be communicated, available to, and understood and implemented by, the appropriate personnel. The elements of this system should be documented, e.g. in a quality manual, for the organization as a whole and/or for a laboratory within the organization.

Note: Quality control laboratories of a manufacturer may have this information in other documents than a quality manual.

2.2 The quality manual should contain as a minimum:

- (a) a quality policy statement, including at least the following:
 - (i) a statement of the laboratory management's intentions with respect to the standard of service it will provide,
 - (ii) a commitment to establishing, implementing and maintaining an effective quality management system,
 - (iii) the laboratory management's commitment to good professional practice and quality of testing, calibration, validation and verification,
 - (iv) the laboratory management's commitment to compliance with the content of these guidelines,
 - (v) a requirement that all personnel concerned with testing and calibration activities within the laboratory familiarize themselves with the documentation concerning quality and the implementation of the policies and procedures in their work;
- (b) the structure of the laboratory (organizational chart);
- (c) the operational and functional activities pertaining to quality, so that the extent and the limits of the responsibilities are clearly defined;
- (d) outline of the structure of documentation used in the laboratory quality management system;
- (e) the general internal quality management procedures;
- (f) references to specific procedures for each test;
- (g) information on the appropriate qualifications, experience and competencies that personnel are required to possess;
- (h) information on initial and in-service training of staff;
- (i) a policy for internal and external audit;
- (j) a policy for implementing and verifying corrective and preventive actions;
- (k) a policy for dealing with complaints;
- (l) a policy for performing management reviews of the quality management system;

- (m) a policy for selecting, establishing and approving analytical procedures;
 - (n) a policy for handling of OOS results;
 - (o) a policy for the employment of appropriate reference substances and reference materials;
 - (p) a policy for participation in appropriate proficiency testing schemes and collaborative trials and the evaluation of the performance (applicable to national pharmaceutical quality control laboratories, but may be applied by other laboratories); and
 - (q) a policy to select service providers and suppliers.
- 2.3 The laboratory should establish, implement and maintain authorized written SOPs including, but not limited to, administrative and technical operations, such as:
- (a) personnel matters, including qualifications, training, clothing and hygiene;
 - (b) the change control;
 - (c) internal audit;
 - (d) dealing with complaints;
 - (e) implementation and verification of corrective and preventive actions;
 - (f) the purchase and receipt of consignments of materials (e.g. samples, reagents);
 - (g) the procurement, preparation and control of reference substances and reference materials (8);
 - (h) the internal labelling, quarantine and storage of materials;
 - (i) the qualification of equipment (11);
 - (j) the calibration of equipment;
 - (k) preventive maintenance and verification of instruments and equipment;
 - (l) sampling, if performed by the laboratory, and visual inspection;
 - (m) the testing of samples with descriptions of the methods and equipment used;
 - (n) atypical and OOS results;
 - (o) validation of analytical procedures;
 - (p) cleaning of laboratory facilities, including bench tops, equipment, work stations, clean rooms (aseptic suites) and glassware;
 - (q) monitoring of environmental conditions, e.g. temperature and humidity;
 - (r) monitoring storage conditions;
 - (s) disposal of reagents and solvent samples; and
 - (t) safety measures.

- 2.4 The activities of the laboratory should be systematically and periodically audited (internally and, where appropriate, by external audits or inspections) to verify compliance with the requirements of the quality management system and to apply corrective and preventive actions, if necessary. The audits should be carried out by trained and qualified personnel, who are independent of the activity to be audited. The quality manager is responsible for planning and organizing internal audits addressing all elements of the quality management system. Such audits should be recorded, together with details of any corrective and preventive action taken.
- 2.5 Management review of quality issues should be regularly undertaken (at least annually), including:
 - (a) reports on internal and external audits or inspections and any follow-up required to correct any deficiencies;
 - (b) the outcome of investigations carried out as a result of complaints received, doubtful (atypical) or aberrant results reported in collaborative trials and/or proficiency tests; and
 - (c) corrective actions applied and preventive actions introduced as a result of these investigations.

3. Control of documentation

- 3.1 Documentation is an essential part of the quality management system. The laboratory should establish and maintain procedures to control and review all documents (both internally generated and from external sources) that form part of the quality documentation. A master list identifying the current version status and distribution of documents should be established and readily available.
- 3.2 The procedures should ensure that:
 - (a) each document, whether a technical or a quality document, has a unique identifier, version number and date of implementation;
 - (b) appropriate, authorized SOPs are available at the relevant locations, e.g. near instruments;
 - (c) documents are kept up to date and reviewed as required;
 - (d) any invalid document is removed and replaced with the authorized, revised document with immediate effect;
 - (e) a revised document includes references to the previous document;
 - (f) old, invalid documents are retained in the archives to ensure traceability of the evolution of the procedures; any copies are destroyed;

- (g) all relevant staff are trained for the new and revised SOPs; and
 - (h) quality documentation, including records, is retained for a minimum of five years.
- 3.3 A system of change control should be in place to inform staff of new and revised procedures. The system should ensure that:
- (a) revised documents are prepared by the initiator, or a person who performs the same function, reviewed and approved at the same level as the original document and subsequently released by the quality manager (quality unit); and
 - (b) staff acknowledge by a signature that they are aware of applicable changes and their date of implementation.

4. Records

- 4.1 The laboratory should establish and maintain procedures for the identification, collection, indexing, retrieval, storage, maintenance and disposal of and access to all quality and technical/scientific records.
- 4.2 All original observations, including calculations and derived data, calibration, validation and verification records and final results, should be retained on record for an appropriate period of time in accordance with national regulations and, if applicable, contractual arrangements, whichever is longer. The records should include the data recorded in the analytical worksheet by the technician or analyst on consecutively numbered pages with references to the appendices containing the relevant recordings, e.g. chromatograms and spectra. The records for each test should contain sufficient information to permit the tests to be repeated and/or the results to be recalculated, if necessary. The records should include the identity of the personnel involved in the sampling, preparation and testing of the samples. The records of samples to be used in legal proceedings should be kept according to the legal requirements applicable to them.

Note: The generally accepted retention period of shelf-life plus one year for a pharmaceutical product on the market and 15 years for an investigational product is recommended, unless national regulations are more stringent or contractual arrangements do not require otherwise.

- 4.3 All quality and technical/scientific records (including analytical test reports, certificates of analysis and analytical worksheets) should be legible, readily retrievable, stored and retained within facilities that provide a suitable environment that will prevent modification, damage or deterioration and/or loss. The conditions

under which all original records are stored should be such as to ensure their security and confidentiality and access to them should be restricted to authorized personnel. Electronic storage and signatures may also be employed but with restricted access and in conformance with requirements for electronic records (12–16).

- 4.4 Quality management records should include reports from internal (and external if performed) audits and management reviews, as well as records of all complaints and their investigations, including records of possible corrective and preventive actions.

5. Data-processing equipment

- 5.1 Detailed recommendations are provided in Appendix 5 to Annex 4 of the *Fortieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations: Supplementary guidelines in good manufacturing practice: validation. Validation of computerized systems* (12).
- 5.2 For computers, automated tests or calibration equipment, and the collection, processing, recording, reporting, storage or retrieval of test and/or calibration data, the laboratory should ensure that:
 - (a) computer software developed by the user is documented in sufficient detail and appropriately validated or verified as being suitable for use;
 - (b) procedures are established and implemented for protecting the integrity of data. Such procedures should include, but are not limited to, measures to ensure the integrity and confidentiality of data entry or collection and the storage, transmission and processing of data. In particular, electronic data should be protected from unauthorized access and an audit trail of any amendments should be maintained;
 - (c) computers and automated equipment are maintained so as to function properly and are provided with the environmental and operating conditions necessary to ensure the integrity of test and calibration data;
 - (d) procedures are established and implemented for making, documenting and controlling changes to information stored in computerized systems; and
 - (e) electronic data should be backed up at appropriate regular intervals according to a documented procedure. Backed-up data should be retrievable and stored in such a manner as to prevent data loss.

Note: For further guidance on validation of data-processing equipment, refer to documents published by the International Society for Pharmaceutical Engineering (13, 14), US Food and Drug Administration (15), European Commission (16) and the Official Medicines Control Laboratories Network of the Council of Europe (17).

6. Personnel

- 6.1 The laboratory should have sufficient personnel with the necessary education, training, technical knowledge and experience for their assigned functions.
- 6.2 The technical management should ensure the competence of all personnel operating specific equipment, instruments or other devices, who are performing tests and/or calibrations, validations or verifications. Their duties also involve the evaluation of results as well as signing analytical test reports and certificates of analysis (see Part three, sections 18.7–18.11 and 19).
- 6.3 Staff undergoing training should be appropriately supervised and should be assessed on completion of the training. Personnel performing specific tasks should be appropriately qualified in terms of their education, training and experience, as required.
- 6.4 The laboratory personnel should be permanently employed or under contract. The laboratory should ensure that additional technical and key support personnel who are under contract are supervised and sufficiently competent and that their work is in accordance with the quality management system.
- 6.5 The laboratory should maintain current job descriptions for all personnel involved in tests and/or calibrations, validations and verifications. The laboratory should also maintain records of all technical personnel, describing their qualifications, training and experience.
- 6.6 The laboratory should have the following managerial and technical personnel:
 - (a) a head of laboratory (supervisor), who should have qualifications appropriate to the position, with extensive experience in medicines analysis and laboratory management in a pharmaceutical quality control laboratory in the regulatory sector or in industry. The head of laboratory is responsible for the content of certificates of analysis and analytical testing reports. This person is also responsible for ensuring that:
 - (i) all key members of the laboratory staff have the requisite competence for the required functions and their grades reflect their responsibilities,
 - (ii) the adequacy of existing staffing, management and training procedures is reviewed periodically,
 - (iii) the technical management is adequately supervised;

- (b) the technical management who ensure that:
 - (i) procedures for performing calibration, verification and (re-) qualification of instruments, monitoring of environmental and storage conditions are in place and are conducted as required,
 - (ii) regular in-service training programmes to update and extend the skills of both professionals and technicians are arranged,
 - (iii) the safekeeping of any materials subject to poison regulation or to the controls applied to narcotic and psychotropic substances (see Part one, section 7.12) kept in the workplace is under the supervision of an authorized person,
 - (iv) national pharmaceutical quality control laboratories regularly participate in suitable proficiency testing schemes and collaborative trials to assess analytical procedures or reference substances;
- (c) analysts, who should normally be graduates in pharmacy, analytical chemistry, microbiology or other relevant subjects, with the requisite knowledge, skills and ability to adequately perform the tasks assigned to them by management and to supervise technical staff;
- (d) technical staff, who should hold diplomas in their subjects awarded by technical or vocational schools; and
- (e) a quality manager (see Part one, section 1.3(j)).

7. Premises

- 7.1 The laboratory facilities are to be of a suitable size, construction and location. These facilities are to be designed to suit the functions and operations to be conducted in them. Rest and refreshment rooms should be separate from laboratory areas. Changing areas and toilets should be easily accessible and appropriate for the number of users.
- 7.2 The laboratory facilities should have adequate safety equipment located appropriately and measures should be in place to ensure good housekeeping. Each laboratory should be equipped with adequate instruments and equipment, including work benches, work stations and fume hoods.
- 7.3 The environmental conditions, including lighting, energy sources, temperature, humidity and air pressure, are to be appropriate to the functions and operations to be performed. The laboratory should ensure that the environmental conditions are monitored, controlled and documented and do not invalidate the results or adversely affect the quality of the measurements.

- 7.4 Special precautions should be taken and, if necessary, there should be a separate and dedicated unit or equipment (e.g. isolator, laminar flow work bench) to handle, weigh and manipulate highly toxic substances, including genotoxic substances. Procedures should be in place to avoid exposure and contamination.
- 7.5 Archive facilities should be provided to ensure the secure storage and retrieval of all documents. The design and condition of the archives should be such as to protect the contents from deterioration. Access to the archives should be restricted to designated personnel.
- 7.6 Procedures should be in place for the safe removal of types of waste including toxic waste (chemical and biological), reagents, samples, solvents and air filters.
- 7.7 Microbiological testing, if performed, should be contained in an appropriately designed and constructed laboratory unit. For further guidance see the draft working document *WHO guideline on good practices for pharmaceutical microbiology laboratories* (reference QAS/09.297).
- 7.8 If in vivo biological testing (e.g. rabbit pyrogen test) is included in the scope of the laboratory activities then the animal houses should be isolated from the other laboratory areas with a separate entrance and air-conditioning system. The relevant guidance and regulations are to be applied (18).

Laboratory storage facilities

- 7.9 The storage facilities should be well organized for the correct storage of samples, reagents and equipment.
- 7.10 Separate storage facilities should be maintained for the secure storage of samples, retained samples (see Part three, section 20), reagents and laboratory accessories (see Part two, sections 10.13–10.14), reference substances and reference materials (see Part two, section 11). Storage facilities should be equipped to store material, if necessary, under refrigeration (2–8°C) and frozen (-20°C) and securely locked. All specified storage conditions should be controlled, monitored and records maintained. Access should be restricted to designated personnel.
- 7.11 Appropriate safety procedures should be drawn up and rigorously implemented wherever toxic or flammable reagents are stored or used. The laboratory should provide separate rooms or areas for storing flammable substances, fuming and concentrated acids and bases, volatile amines and other reagents, such as hydrochloric acid, nitric acid, ammonia and bromine. Self-igniting materials, such as metallic sodium and potassium, should also be stored separately. Small stocks of acids, bases and solvents may be kept in the laboratory store but the main stocks of these items should preferably be retained in a store separate from the laboratory building.

- 7.12 Reagents subject to poison regulations or to the controls applied to narcotic and psychotropic substances should be clearly marked as required by national legislation. They should be kept separately from other reagents in locked cabinets. A designated responsible member of staff should maintain a register of these substances. The head of each unit should accept personal responsibility for the safekeeping of any of these reagents kept in the workplace.
- 7.13 Gases also should be stored in a dedicated store, if possible isolated from the main building. Wherever possible gas bottles in the laboratory are to be avoided and distribution from an external gas store is preferred. If gas bottles are present in the laboratory they should be safely secured.

Note: Consideration should be given to the installation of gas generators.

8. Equipment, instruments and other devices

- 8.1 Equipment, instruments and other devices should be designed, constructed, adapted, located, calibrated, qualified, verified and maintained as required by the operations to be carried out in the local environment. The user should purchase the equipment from an agent capable of providing full technical support and maintenance when necessary.
- 8.2 The laboratory should have the required test equipment, instruments and other devices for the correct performance of the tests and/or calibrations, validations and verifications (including the preparation of samples and the processing and analysis of test and/or calibration data).
- 8.3 Equipment, instruments and other devices, including those used for sampling, should meet the laboratory's requirements and comply with the relevant standard specifications, as well as being verified, qualified and/or calibrated regularly (see Part two, section 12).

9. Contracts

Purchasing services and supplies

- 9.1 The laboratory should have a procedure for the selection and purchasing of services and supplies it uses that affect the quality of testing.
- 9.2 The laboratory should evaluate suppliers of critical consumables, supplies and services which affect quality of testing, maintain records of these evaluations and list approved suppliers, which have been demonstrated to be of a suitable quality with respect to the requirements of the laboratory.

Subcontracting of testing

- 9.3 When a laboratory subcontracts work, which may include specific testing, it is to be done with organizations approved for the type of activity required. The laboratory is responsible for periodically assessing the competence of a contracted organization.
- 9.4 When a laboratory performs testing for a customer and subcontracts part of the testing, it should advise the customer of the arrangement in writing and, if appropriate, gain his or her approval.
- 9.5 There should be a written contract which clearly establishes the duties and responsibilities of each party, defines the contracted work and any technical arrangements made in connection with it. The contract should permit the laboratory to audit the facilities and competencies of the contracted organization and ensure the access of the laboratory to records and retained samples.
- 9.6 The contracted organization should not pass to a third party any work entrusted to it under contract without the laboratory's prior evaluation and approval of the arrangements.
- 9.7 The laboratory should maintain a register of all subcontractors that it uses and a record of the assessment of the competence of subcontractors.
- 9.8 The laboratory takes the responsibility for all results reported, including those furnished by the subcontracting organization.

Part two. Materials, equipment, instruments and other devices

10. Reagents

- 10.1 All reagents and chemicals, including solvents and materials used in tests and assays, should be of appropriate quality.
- 10.2 Reagents should be purchased from reputable, approved suppliers and should be accompanied by the certificate of analysis, and the material safety data sheet, if required.
- 10.3 In the preparation of reagent solutions in the laboratory:
 - (a) responsibility for this task should be clearly specified in the job description of the person assigned to carry it out; and

- (b) prescribed procedures should be used which are in accordance with published pharmacopoeial or other standards where available. Records should be kept of the preparation and standardization of volumetric solutions.

10.4 The labels of all reagents should clearly specify:

- (a) content;
- (b) manufacturer;
- (c) date received and date of opening of the container;
- (d) concentration, if applicable;
- (e) storage conditions; and
- (f) expiry date or retest date, as justified.

10.5 The labels of reagent solutions prepared in the laboratory should clearly specify:

- (a) name;
- (b) date of preparation and initials of technician or analyst;
- (c) expiry date or retest date, as justified; and
- (d) concentration, if applicable.

10.6 The labels for volumetric solutions prepared in the laboratory should clearly specify:

- (a) name;
- (b) molarity (or concentration);
- (c) date of preparation and initials of technician/analyst;
- (d) date of standardization and initials of technician/analyst; and
- (e) standardization factor.

Note: The laboratory should ensure that the volumetric solution is suitable for use at the time of use.

10.7 In the transportation and subdivision of reagents:

- (a) whenever possible they should be transported in the original containers; and
- (b) when subdivision is necessary, clean containers should be used and appropriately labelled.

Visual inspection

- 10.8 All reagent containers should be visually inspected to ensure that the seals are intact, both when they are delivered to the store and when they are distributed to the units.
- 10.9 Reagents that appear to have been tampered with should be rejected; however, this requirement may exceptionally be waived if the identity and purity of the reagent concerned can be confirmed by testing.

Water

- 10.10 Water should be considered as a reagent. The appropriate grade for a specific test should be used as described in the pharmacopoeias or in an approved test when available.
- 10.11 Precautions should be taken to avoid contamination during its supply, storage and distribution.
- 10.12 The quality of the water should be verified regularly to ensure that the various grades of water meet the appropriate specifications.

Storage

- 10.13 Stocks of reagents should be maintained in a store under the appropriate storage conditions (ambient temperature, under refrigeration or frozen). The store should contain a supply of clean bottles, vials, spoons, funnels and labels, as required, for dispensing reagents from larger to smaller containers. Special equipment may be needed for the transfer of larger volumes of corrosive liquids.
- 10.14 The person in charge of the store is responsible for looking after the storage facilities and their inventory and for noting the expiry date of chemicals and reagents. Training may be needed in handling chemicals safely and with the necessary care.

11. Reference substances and reference materials

- 11.1 Reference substances (primary reference substances or secondary reference substances (8)) are used for the testing of a sample.

Note: Pharmacopoeial reference substances should be employed when available and appropriate for the analysis. When a pharmacopoeia reference substance has not been established then the manufacturer should use its own reference substance.

- 11.2 Reference materials may be necessary for the calibration and/or qualification of equipment, instruments or other devices.

Registration and labelling

- 11.3 An identification number should be assigned to all reference substances, except for pharmacopoeial reference substances.
- 11.4 A new identification number should be assigned to each new batch.
- 11.5 This number should be marked on each vial of the reference substance.
- 11.6 The identification number should be quoted on the analytical worksheet every time the reference substance is used (see Part three, section 15.5). In the case of pharmacopoeial reference substances the batch number and/or the batch validity statement should be attached to the worksheet.
- 11.7 The register for all reference substances and reference materials should be maintained and contain the following information:
 - (a) the identification number of the substance or material;
 - (b) a precise description of the substance or material;
 - (c) the source;
 - (d) the date of receipt;
 - (e) the batch designation or other identification code;
 - (f) the intended use of the substance or material (e.g. as an infrared reference substance or as an impurity reference substance for thin-layer chromatography);
 - (g) the location of storage in the laboratory, and any special storage conditions;
 - (h) any further necessary information (e.g. the results of visual inspections);
 - (i) expiry date or retest date;
 - (j) certificate (batch validity statement) of a pharmacopoeial reference substance and a certified reference material which indicates its use, the assigned content, if applicable, and its status (validity); and
 - (k) in the case of secondary reference substances prepared and supplied by the manufacturer, the certificate of analysis.
- 11.8 A person should be nominated to be responsible for reference substances and reference materials.
- 11.9 If a national pharmaceutical quality control laboratory is required to establish reference substances for use by other institutions, a separate reference substances unit should be established.

- 11.10 In addition a file should be kept in which all information on the properties of each reference substance is entered including the safety data sheets.
- 11.11 For reference substances prepared in the laboratory, the file should include the results of all tests and verifications used to establish the reference substances and expiry date or retest date; these should be signed by the responsible analyst.

Retesting (monitoring)

- 11.12 All reference substances prepared in the laboratory or supplied externally should be retested at regular intervals to ensure that deterioration has not occurred. The interval for retesting depends on a number of factors, including stability of the substance, storage conditions employed, type of container and extent of use (how often the container is opened and closed). More detailed information on the handling, storage and retesting of reference substances is given in the *WHO General guidelines for the establishment, maintenance and distribution of chemical reference substances* (8).
- 11.13 The results of these tests should be recorded and signed by the responsible analyst.
- 11.14 In the case that the result of retesting of a reference substance is non-compliant, a retrospective check of tests performed using this reference substance since its previous examination should be carried out. For evaluation of outcomes of retrospective checks and consideration of possible corrective actions, risk analysis should be applied.
- 11.15 Pharmacopoeial reference substances are regularly retested and the validity (current status) of these reference substances is available from the issuing pharmacopoeia by various means, e.g. web sites or catalogues. Retesting by the laboratory is not necessary, provided the reference substances are stored in accordance with the storage conditions indicated.

12. Calibration, verification of performance and qualification of equipment, instruments and other devices

- 12.1 Each item of equipment, instrument or other device used for testing, verification and/or calibration should, when practicable, be uniquely identified.
- 12.2 All equipment, instruments and other devices (e.g. volumetric glassware and automatic dispensers) requiring calibration should be labelled, coded or otherwise identified to indicate the status of calibration and the date when recalibration is due.

- 12.3 Laboratory equipment should undergo design qualification, installation qualification, operation qualification and performance qualification (for definitions of these terms see the Glossary) (11). Depending on the function and operation of the instrument, the design qualification of a commercially available standard instrument may be omitted as the installation qualification, operational qualification and performance qualification may be considered to be a sufficient indicator of its suitable design.
- 12.4 As applicable, the performance of equipment should be verified at appropriate intervals according to a plan established by the laboratory.
- 12.5 Measuring equipment should be regularly calibrated according to a plan established by the laboratory (11).
- 12.6 Specific procedures should be established for each type of measuring equipment, taking into account the type of equipment, the extent of use and supplier's recommendations. For example:
- pH meters are verified with standard certified buffer solutions before use;
 - balances are to be checked daily using internal calibration and regularly using suitable test weights, and requalification should be performed annually using certified reference weights.
- 12.7 Only authorized personnel should operate equipment, instruments and devices. Up-to-date SOPs on the use, maintenance, verification, qualification and calibration of equipment, instruments and devices (including any relevant manuals provided by the manufacturer) should be readily available for use by the appropriate laboratory personnel together with a schedule of the dates on which verification and/or calibration is due.
- 12.8 Records should be kept of each item of equipment, instrument or other device used to perform testing, verification and/or calibration. The records should include at least the following:
- (a) the identity of the equipment, instrument or other device;
 - (b) the manufacturer's name and the equipment model, serial number or other unique identification;
 - (c) the qualification, verification and/or calibration required;
 - (d) the current location, where appropriate;
 - (e) the equipment manufacturer's instructions, if available, or an indication of their location;
 - (f) the dates, results and copies of reports, verifications and certificates of all calibrations, adjustments, acceptance criteria and the due date of the next qualification, verification and/or calibration;

- (g) the maintenance carried out to date and the maintenance plan; and
- (h) a history of any damage, malfunction, modification or repair.

It is also recommended that records should be kept and additional observations made of the time for which the equipment, instruments or devices were used.

- 12.9 Procedures should include instructions for the safe handling, transport and storage of measuring equipment. On reinstallation, requalification of the equipment is required to ensure that it functions properly.
- 12.10 Maintenance procedures should be established, e.g. regular servicing should be performed by a team of maintenance specialists, whether internal or external, followed by verification of performance.
- 12.11 Equipment, instruments and other devices, either subjected to overloading or mishandling, giving suspect results, shown to be defective or outside specified limits, should be taken out of service and clearly labelled or marked. Wherever possible they should not be used until they have been repaired and requalified.
- 12.12 When the equipment, instruments and other devices are outside the direct control of the laboratory for a certain period or have undergone major repair, the laboratory should requalify the equipment to ensure its suitability for use.

Note: For further guidance on calibration, verification of performance and qualification of equipment refer to:

- *Procedures for verifying and calibrating refractometers, thermometers used in determinations of melting temperatures and potentiometers for pH determinations and methods for verifying the reliability of scales for ultraviolet and infrared spectrophotometers and spectrofluorometers in The International Pharmacopoeia (19);*
- *Specific guidelines for qualification of equipment elaborated by the European Network of Official Medicines Control Laboratories (OMCL) (20); and*
- *General chapter of the US Pharmacopeia on Analytical instrument qualification (21).*

13. Traceability

- 13.1 The result of an analysis should be traceable, when appropriate, ultimately to a primary reference substance.
- 13.2 All calibrations or qualification of instruments should be traceable to certified reference materials and to SI units (metrological traceability).

Part Three. Working procedures

14. Incoming samples

Sections 14.1–14.3 are applicable to national pharmaceutical quality control laboratories.

- 14.1 Samples received by a laboratory may be for compliance testing or for investigative testing. Samples for compliance testing include routine samples for control, samples suspected of not complying with the specifications or samples submitted in connection with a marketing authorization process. Close collaboration with the providers of the samples is important. In particular it is important that the sample is large enough to enable, if required, a number of replicate tests to be carried out (see Part three, section 14.3) and for part of the sample to be retained (see Part three, section 20).
- 14.2 Samples for investigative testing may be submitted by various sources including customs, police and medicines inspectors. These samples comprise suspicious, illegal or counterfeit substances or products. Usually, the primary objective of investigative testing is to identify the substance or the ingredient in the product and, if sufficient substance or product is available, to estimate the purity or content. Well-documented screening procedures should be in place as well as confirmatory analytical procedures to positively identify the substance or the ingredient(s). If an estimation of the content of an identified ingredient is required then an appropriate quantitative analytical procedure should be applied. The value obtained should be reported with an indication of the uncertainty of measurement if required (see Part three, section 18.10).
- 14.3 It is common for a sample to be taken and divided into three approximately equal portions for submission to the laboratory:
- one for immediate testing;
 - the second for confirmation of testing if required; and
 - the third for retention in case of dispute.
- 14.4 If the laboratory is responsible for sampling of substances, materials or products for subsequent testing then it should have a sampling plan and an internal procedure for sampling available to all analysts and technicians working in the laboratory. Samples should be representative of the batches of material from which they are taken and sampling should be carried out so as to avoid contamination and other adverse effects on quality, or mix-up of or by the material being sampled. All the relevant data related to sampling should be recorded.

Note: Guidelines for sampling of pharmaceutical products and related materials were adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-ninth meeting (22).

Test request

- 14.5 A standard test request form should be filled out and should accompany each sample submitted to the laboratory. In the case of a pharmaceutical manufacturer's laboratory the requirements may be given in the master production instructions.
- 14.6 The test request form should provide or leave space for the following information:
- (a) the name of the institution or inspector that supplied the sample;
 - (b) the source of the material;
 - (c) a full description of the medicine, including its composition, international nonproprietary name (INN) (if available) and brand name(s);
 - (d) dosage form and concentration or strength, the manufacturer, the batch number (if available) and the marketing authorization number;
 - (e) the size of the sample;
 - (f) the reason for requesting the analysis;
 - (g) the date on which the sample was collected;
 - (h) the size of the consignment from which it was taken, when appropriate;
 - (i) the expiry date (for pharmaceutical products) or retest date (for APIs and pharmaceutical excipients);
 - (j) the specification to be used for testing;
 - (k) a record of any further comments (e.g. discrepancies found or associated hazard); and
 - (l) the required storage conditions.

14.7 The laboratory should review the test request to ensure that:

- (a) the requirements are adequately defined and the laboratory has the capability and resources to meet them; and
- (b) the appropriate tests and/or methods are selected and are capable of meeting customers' requirements.

Any issue should be resolved with the originator of the request for analysis before testing starts and a record of the review should be kept.

Registration and labelling

- 14.8 All newly delivered samples and accompanying documents (e.g. the test request) should be assigned a registration number. Separate registration numbers should be assigned to requests referring to two or more medicines, different dosage forms, or different batches of the same medicine or different sources of the same batch. If applicable, a unique registration number should also be assigned to any incoming retained sample (see Part three, section 20).

- 14.9 A label bearing the registration number should be affixed to each container of the sample. Care should be taken to avoid obscuring any other markings or inscriptions.
- 14.10 A register should be kept, which may be a record book, a card file or data-processing equipment, in which the following information is recorded:
 - (a) the registration number of the sample;
 - (b) the date of receipt; and
 - (c) the specific unit to which the sample was forwarded.

Visual inspection of the submitted sample

- 14.11 The sample received should be visually inspected by laboratory staff to ensure that the labelling conforms with the information contained in the test request. The findings should be recorded, dated and signed. If discrepancies are found, or if the sample is obviously damaged, this fact should be recorded without delay on the test request form. Any queries should be immediately referred back to the provider of the sample.

Storage

- 14.12 The sample prior to testing, the retained sample (see Part three, section 20) and any portions of the sample remaining after performance of all the required tests should be stored safely, taking into account the storage conditions (22, 23) specified for the sample.

Forwarding to testing

- 14.13 The specific unit to which the sample is sent for testing is determined by the person responsible.
- 14.14 The examination of a sample should not be started before the relevant test request has been received.
- 14.15 The sample should be properly stored until all relevant documentation has been received.
- 14.16 A request for analysis may be accepted verbally only in emergencies. All details should immediately be placed on record pending the receipt of written confirmation.
- 14.17 Unless a computerized system is used, copies or duplicates of all documentation should accompany each numbered sample when sent to the specific unit.
- 14.18 Testing should be performed as described under Part three, section 17.

15. Analytical worksheet

15.1 The analytical worksheet is an internal document to be used by the analyst for recording information about the sample, the test procedure, calculations and the results of testing. It is to be complemented by the raw data obtained in the analysis.

Purpose

15.2 The analytical worksheet contains documentary evidence either:

- to confirm that the sample being examined is in accordance with the requirements; or
- to support an OOS result (see Part three, sections 18.1–18.3).

Use

15.3 A separate analytical worksheet should usually be used for each numbered sample or group of samples.

15.4 Analytical worksheets from different units relating to the same sample should be assembled together.

Content

15.5 The analytical worksheet should provide the following information:

- (a) the registration number of the sample (see Part three, section 14.9);
- (b) page numbering, including the total number of pages (and including annexes);
- (c) the date of the test request;
- (d) the date on which the analysis was started and completed;
- (e) the name and signature of the analyst;
- (f) a description of the sample received;
- (g) references to the specifications and a full description of test methods by which the sample was tested, including the limits;
- (h) the identification of the test equipment used (see Part two, section 12.1);
- (i) the identification number of any reference substance used (see Part two, section 11.5);
- (j) if applicable, the results of the system suitability test;
- (k) the identification of reagents and solvents employed;
- (l) (the results obtained;

- (m) the interpretation of the results and the final conclusions (whether or not the sample was found to comply with the specifications), approved and signed by the supervisor; and
 - (n) any further comments, for example, for internal information (see Part three, section 17.1), or detailed notes on the specifications selected and the methods of assessment used (see Part three, section 15.9), or any deviation from the prescribed procedure, which should be approved and reported, or whether and when portions of the sample were forwarded to other units for special tests and the date on which the results were received.
- 15.6 All values obtained from each test, including blank results, should immediately be entered on the analytical worksheet and all graphical data, whether obtained from recording instruments or plotted by hand, should be attached or be traceable to an electronic record file or document where the data are available.
- 15.7 The completed analytical worksheet should be signed by the responsible analyst(s), verified and approved and signed by the supervisor.
- 15.8 When a mistake is made in an analytical worksheet or when data or text need to be amended, the old information should be deleted by putting a single line through it (it should not be erased or made illegible) and the new information added alongside. All such alterations should be signed by the person making the correction and the date of the change inserted. The reason for the change should also be given on the worksheet (suitable procedures should be in place for amending electronic worksheets).
- Selection of the specifications to be used***
- 15.9 The specification necessary to assess the sample may be that given in the test request or master production instructions. If no precise instruction is given, the specification in the officially recognized national pharmacopoeia may be used or, failing this, the manufacturer's officially approved or other nationally recognized specification. If no suitable method is available:
- (a) the specification contained in the marketing authorization or product licence may be requested from the marketing authorization holder or manufacturer and verified by the laboratory; or
 - (b) the requirements may be set by the laboratory itself on the basis of published information and any procedure employed is to be validated by the testing laboratory (see Part three, section 16).
- 15.10 For official specifications the current version of the relevant pharmacopoeia should be available.

Filing

15.11 The analytical worksheet should be kept safely together with any attachments, including calculations and recordings of instrumental analyses.

16. Validation of analytical procedures

- 16.1 All analytical procedures employed for testing should be suitable for the intended use. This is demonstrated by validation (24). Validation also serves to establish acceptance criteria for system suitability tests which are subsequently employed for the verification of the analytical procedure before analysis.
- 16.2 Validation should be performed according to a validation protocol, which includes analytical performance characteristics to be verified for various types of analytical procedures. Typical characteristics which should be considered are listed in Table 1 (in the development phase of an analytical procedure, robustness, i.e. the ability of the procedure to provide results of acceptable accuracy and precision under a variety of conditions should also be considered). The results are to be documented in the validation report.

Table 1
Characteristics to consider during validation of analytical procedures

Type of analytical Procedure	Identification	Testing for impurities		<ul style="list-style-type: none"> • dissolution (measurement only) • content/potency
		Quantitative tests	Limit tests	
Characteristics				
Accuracy	–	+	–	+
Precision				
Repeatability	–	+	–	+
Intermediate precision ^a	–	+	–	+
Specificity	+	+	+	+
Detection limit	–	– ^b	+	–
Quantitation limit	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

– Characteristic is normally not evaluated; + characteristic should normally be evaluated.

^a In cases where a reproducibility study has been performed, intermediate precision is not needed.

^b May be needed in some cases.

- 16.3 Pharmacopoeial methods are considered to be validated for the intended use as prescribed in the monograph(s). However, the laboratory should also confirm that, for example, for a particular finished pharmaceutical product (FPP) examined for the first time, no interference arises from the excipients present, or that for an API, impurities coming from a new route of synthesis are adequately differentiated. If the pharmacopoeial method is adapted for another use then it should be validated for such a use to demonstrate that it is fit-for-purpose.
- 16.4 System suitability testing is an integral part of many analytical procedures. The tests are based on the fact that the equipment, electronics, analytical operations and samples to be analysed contribute to the system. Which system suitability tests are to be applied depends on the type of procedure to be used. System suitability tests are employed for the verification of pharmacopoeial methods or validated analytical procedures and should be performed prior to the analysis. Provided the system suitability criteria are fulfilled the method or procedure is considered to be suitable for the intended purpose.

Note: If a large number of samples is being analysed in sequence, then appropriate system suitability tests are to be performed throughout the sequence to demonstrate that the performance of the procedure is satisfactory.

Verification is not required for basic pharmacopoeial methods such as (but not limited to) pH, loss on drying and wet chemical methods.

- 16.5 A major change to the analytical procedure, or in the composition of the product tested, or in the synthesis of the API, will require revalidation of the analytical procedure.

Note: Further guidance on validation of analytical procedures is available in the following:

- *Guideline elaborated by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (25);*
- *Guideline elaborated by the European Network of Official Medicines Control Laboratories (OMCL) (26);*
- *General chapters of the US Pharmacopeia on Validation of compendial procedures and on Verification of compendial procedures (27).*

17. Testing

- 17.1 The sample should be tested in accordance with the work plan of the laboratory after completion of the preliminary procedures. If this is not feasible the reasons

should be noted, e.g. in the analytical worksheet (see Part three, section 15), and the sample should be stored in a special place which is kept locked (see Part three, section 14.12).

- 17.2 Specific tests required may need to be carried out by another unit or by a specialized external laboratory (see Part one, section 9). The responsible person should prepare the request and arrange for the transfer of the required number of units (bottles, vials or tablets) from the sample. Each of these units should bear the correct registration number. When the analytical test report contains results of tests performed by subcontractors, these results should be identified as such.
- 17.3 Detailed guidance on official pharmacopoeial requirements is usually given in the general notices and specific monographs of the pharmacopoeia concerned. Test procedures should be described in detail and should provide sufficient information to allow properly trained analysts to perform the analysis in a reliable manner. Where system suitability criteria are defined in the method they should be fulfilled. Any deviation from the test procedure should be approved and documented.

18. Evaluation of test results

- 18.1 Test results should be reviewed and, where appropriate, evaluated statistically after completion of all the tests to determine whether they are mutually consistent and if they meet the specifications used. The evaluation should take into consideration the results of all the tests (all test data). Whenever doubtful (atypical) results are obtained they should be investigated. The complete testing procedure needs to be checked according to the internal quality management system (see also Part one, section 2).
- 18.2 When a doubtful result (suspected OOS result) has been identified, a review of the different procedures applied during the testing process is to be undertaken by the supervisor with the analyst or technician before retesting is permitted. The following steps should be followed:
 - (a) confirm with the analyst or technician that the appropriate procedure(s) was (were) applied and followed correctly;
 - (b) examine the raw data to identify possible discrepancies;
 - (c) check all calculations;
 - (d) check that the equipment used was qualified and calibrated, and that system suitability tests were performed and were acceptable;
 - (e) ensure that the appropriate reagents, solvents and reference substances were used;

- (f) confirm that the correct glassware was used; and
 - (g) ensure that original sample preparations are not discarded until the investigation is complete.
- 18.3 The identification of an error which caused an aberrant result will invalidate the result and a retest of the sample will be necessary. Doubtful results can be rejected only if they are clearly due to an identified error. Sometimes the outcome of the investigation is inconclusive — no obvious cause can be identified — in which case a confirmatory determination is to be performed by another analyst who should be at least as experienced and competent in the analytical procedure as the original analyst. A similar value would indicate an OOS result. However, further confirmation using another validated method, if available, may be advised.
- 18.4 An SOP should be in place for the conduct of an investigation of an OOS test result. The SOP should give clear guidance on the number of retests allowed (based on sound statistical principles). All investigations and their conclusions should be recorded. In the event of an error, any corrective action taken and any preventive measure introduced should be recorded and implemented.
- 18.5 All individual results (all test data) with acceptance criteria should be reported.
- 18.6 All conclusions should be entered on the analytical worksheet (see Part three, section 15) by the analyst and signed by the supervisor.

Note: Further guidance on evaluation and reporting of test results is available in the following:

- *Guideline elaborated by the US Food and Drug Administration* (5);
- *Guideline elaborated by the European Network of Official Medicines Control Laboratories* (OMCL) (28).

Analytical test report

- 18.7 The analytical test report is a compilation of the results and states the conclusions of the examination of a sample. It should be:
- (a) issued by the laboratory; and
 - (b) based on the analytical worksheet (see Part three, section 15).
- 18.8 Any amendments to the original analytical test report will require the issue of a new corrected document.
- 18.9 Pharmacopoeial content limits are set taking into account the uncertainty of measurement, and the production capability and acceptance criteria for an

analytical result should be predefined. Under presently applicable rules neither the pharmacopoeias nor the NMRA require the value found to be expressed with its associated expanded uncertainty for compliance testing. However, when reporting the results of investigative testing, although the primary objective is to identify a substance in the sample, a determination of its concentration may be also requested, in which case the estimated uncertainty should also be given.

18.10 Measurement uncertainty can be estimated in a number of ways, e.g.:

- (a) by preparing an uncertainty budget for each uncertainty component identified in an analytical procedure (bottom-up approach);
- (b) from validation data and control charts (29); and
- (c) from the data obtained from proficiency tests or collaborative trials (top-down approach).

Note: Further guidance can be found in various guidelines (9, 10, 30, 31, 32).

Content of the analytical test report

18.11 The analytical test report should provide the following information:

- (a) the laboratory registration number of the sample;
- (b) the laboratory test report number;
- (c) the name and address of the laboratory testing the sample;
- (d) the name and address of the originator of the request for analysis;
- (e) the name, description and batch number of the sample, where appropriate;
- (f) an introduction giving the background to and the purpose of the investigation;
- (g) a reference to the specifications used for testing the sample or a detailed description of the procedures employed (sample for investigative testing), including the limits;
- (h) the results of all the tests performed or the numerical results with the standard deviation of all the tests performed (if applicable);
- (i) a discussion of the results obtained;
- (j) a conclusion as to whether or not the sample(s) was (were) found to be within the limits of the specifications used, or for a sample for investigative testing, the substance(s) or ingredient(s) identified;
- (k) the date on which the test(s) was (were) completed;
- (l) the signature of the head of the laboratory or authorized person;
- (m) the name and address of the original manufacturer and, if applicable, those of the repacker and/or trader;

- (n) whether or not the sample(s) complies (comply) with the requirements;
- (o) the date on which the sample was received;
- (p) the expiry date or retest date, if applicable; and
- (q) a statement indicating that the analytical test report, or any portion thereof, cannot be reproduced without the authorization of the laboratory.

19. Certificate of analysis

19.1 A certificate of analysis is prepared for each batch of a substance or product and usually contains the following information:

- (a) the registration number of the sample;
- (b) date of receipt;
- (c) the name and address of the laboratory testing the sample;
- (d) the name and address of the originator of the request for analysis;
- (e) the name, description and batch number of the sample where appropriate;
- (f) the name and address of the original manufacturer and, if applicable, those of the repacker and/or trader;
- (g) the reference to the specification used for testing the sample;
- (h) the results of all tests performed (mean and standard deviation, if applicable) with the prescribed limits;
- (i) a conclusion as to whether or not the sample was found to be within the limits of the specification;
- (j) expiry date or retest date if applicable;
- (k) date on which the test(s) was (were) completed; and
- (l) the signature of the head of laboratory or other authorized person.

Note: The *Guideline on model certificate of analysis* was adopted by the WHO Expert Committee on Specifications for Pharmaceutical Preparations at its thirty-sixth meeting (3).

20. Retained samples

20.1 Samples should be retained as required by the legislation or by the originator of the request for analysis. There should be a sufficient amount of retained sample to allow at least two re-analyses. The retained sample should be kept in its final pack.

Part four. Safety

21. General rules

- 21.1 General and specific safety instructions reflecting identified risk, should be made available to each staff member and supplemented regularly as appropriate (e.g. with written material, poster displays, audiovisual material and occasional seminars).
- 21.2 General rules for safe working in accordance with national regulations and SOPs normally include the following requirements:
- (a) safety data sheets should be available to staff before testing is carried out;
 - (b) smoking, eating and drinking in the laboratory should be prohibited;
 - (c) staff should be familiar with the use of fire-fighting equipment, including fire extinguishers, fire blankets and gas masks;
 - (d) staff should wear laboratory coats or other protective clothing, including eye protection;
 - (e) special care should be taken, as appropriate, in handling, for example, highly potent, infectious or volatile substances;
 - (f) highly toxic and/or genotoxic samples should be handled in a specially designed facility to avoid the risk of contamination;
 - (g) all containers of chemicals should be fully labelled and include prominent warnings (e.g. “poison”, “flammable”, “radioactive”) whenever appropriate;
 - (h) adequate insulation and spark-proofing should be provided for electrical wiring and equipment, including refrigerators;
 - (i) rules on safe handling of cylinders of compressed gases should be observed and staff should be familiar with the relevant colour identification codes;
 - (j) staff should be aware of the need to avoid working alone in the laboratory; and
 - (k) first-aid materials should be provided and staff instructed in first-aid techniques, emergency care and the use of antidotes.

- 21.3 Protective clothing should be available, including eye protection, masks and gloves. Safety showers should be installed. Rubber suction bulbs should be used on manual pipettes and siphons. Staff should be instructed in the safe handling of glassware, corrosive reagents and solvents and particularly in the use of safety containers or baskets to avoid spillage from containers. Warnings, precautions and instructions should be given for work with violent, uncontrollable or dangerous

reactions when handling specific reagents (e.g. mixing water and acids, or acetone–chloroform and ammonia), flammable products, oxidizing or radioactive agents and especially biologicals such as infectious agents. Peroxide-free solvents should be used. Staff should be aware of methods for the safe disposal of unwanted corrosive or dangerous products by neutralization or deactivation and of the need for safe and complete disposal of mercury and its salts.

- 21.4 Poisonous or hazardous products should be singled out and labelled appropriately, but it should not be taken for granted that all other chemicals and biologicals are safe. Unnecessary contact with reagents, especially solvents and their vapours, should be avoided. The use of known carcinogens and mutagens as reagents should be limited or totally excluded if required by national regulations. Replacement of toxic solvents and reagents by less toxic materials or reduction of their use should always be the aim, particularly when new techniques are developed.

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Appendix

Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

A list of equipment considered by the Committee to be adequate either for a first-stage or medium-sized pharmaceutical quality control laboratory is given in the table. In the case of a medium-sized laboratory, specific sections are devoted to a microbiology unit and pharmacognosy/phytochemistry unit. For a first-stage laboratory testing herbal medicines, the additional equipment recommended is specified in the table.

This list does not represent any requirements which should be fulfilled to comply with these guidelines. NMRA_s or laboratories wishing to perform pharmaceutical analyses may consider the following list in the establishment or upgrading of their testing facilities. For budgetary reasons it is necessary, besides the cost of equipment, to take into consideration the cost of reference materials, reagents, solvents, glassware, other laboratory commodities and personnel. Experience has shown that for sustainability, a laboratory should allow a margin of 10–15% per year of the purchasing expenditure on equipment to cover the cost of maintenance.

Table

Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory

First-stage laboratory	
<i>Equipment and major instrument</i>	<i>Quantity</i>
Top-loading balance	1
Analytical balance (5 digits)	1 or 2
Melting-point apparatus	1
pH meter (with assorted electrodes)	1
Microscope	1
Polarimeter	1
High-performance liquid chromatograph with ultraviolet detector	2
Ultraviolet/visible spectrophotometer	1
Infrared spectrophotometer with pellet press	1
Karl Fischer titrator (semi-micro determination of water)	1
Agate mortar with pestle	1

Table *continued*

First-stage laboratory	
<i>Equipment and major instrument</i>	<i>Quantity</i>
Equipment for thin-layer chromatography	1
Thin-layer chromatography spotter	1
Developing chambers	6 + 1 ^a
Atomizers	6
Ultraviolet viewing lamp	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution apparatus	1
Soxhlet extraction apparatus (60 ml)	3 + 1 ^a
Micrometer callipers	1
Pycnometers	2
Burettes/pipettes (10 ml and 25 ml/1, 2, 5, 10, 20, 25, 50 ml)	3 of each
Desiccator	1 + 1 ^a
Centrifuge (table-top model, 4-place swing rotor)	1
Water-bath (20 litres)	1
Hot plates with magnetic stirrers	3
Vacuum pump (rotary, oil)	1
Drying oven (60 litres)	1
Vacuum oven (17 litres)	1
Muffle furnace	1
Refrigerator (explosion-proof)	1
Water distilling apparatus (8 litres/hour)	1
Water deionizer (10 litres/hour)	1
Dehumidifier (where needed)	1
Fume hood	1
<i>Optional items</i>	
Analytical microbalance	1
Flame photometer (including air compressor)	1
Refractometer	1
Viscometer	1
Vortex mixer	1

Table continued

First-stage laboratory	
Optional items	
Medium-sized laboratory	
Equipment and major instruments	Quantity
Shaker (wrist-action)	1
Pipette rinser	1
Constant temperature water-bath	1
Ultrasonic cleaner (5 litres)	1
Equipment and major instruments	
Top-loading balance	1 or 2
Analytical balance (5 digits)	2
Analytical microbalance	1
Microscope	1 or 2
Equipment for thin-layer chromatography	1
Thin-layer chromatography multispotter	1
Developing chambers	6
Atomizers	6
Ultraviolet viewing lamp	1
Potentiometric titrimeter	1
Micro-Kjeldahl equipment (including fume flasks)	1
Soxhlet extraction apparatus (60 ml)	3
Pycnometers	2
Burettes/pipettes (10 ml and 25 ml/1, 2, 5, 10, 20, 25, 50 ml)	6 of each
Micrometer callipers	1
Heating mantles for flasks (assorted sizes: 50, 200 and 2000 ml)	6
Sieves (assorted sizes)	1 set
Centrifuge (floor model)	1
Shaker (wrist-action)	1
Vortex mixers	2
Water-bath (electrical, 20 litres)	2 or 3
Hot plates with magnetic stirrers	3 or 4
Vacuum pump (rotary, oil)	2
Vacuum rotary evaporator	1

Table continued

Medium-sized laboratory	
<i>Equipment and major instruments</i>	<i>Quantity</i>
Drying oven (60 litres)	2 or 3
Muffle furnace (23 litres)	1
Vacuum oven (17 litres)	1
Desiccators	2
Refrigerator (explosion-proof)	2
Freezer	1
Ultrasonic cleaners (5 litres)	2
Laboratory glassware washing machine	1
Water distilling apparatus (8 litres/hour)	1
Water deionizing equipment (10 litres/hour)	1
Fume hoods	2
Melting-point apparatus	1
Polarimeter	1
pH meters (with assorted electrodes)	2
High-performance liquid chromatograph with variable wavelength	
Ultraviolet/visible detector	3 or 4
Ultraviolet/visible spectrophotometer, double-beam	1
Infrared spectrophotometer with pellet press	1
Agate mortar with pestle	1
Gas chromatograph (flame ionization, direct and static head space injection)	1
Refractometer	1
Karl Fischer titrators (1 semi-micro and 1 coulometric for micro-determination of water)	2
Oxygen flask combustion apparatus	1
Disintegration test equipment (1 basket for 6 tablets)	1
Dissolution test equipment (for 6 tablets/capsules)	1
<i>Optional items</i>	
Atomic absorption spectrophotometer	1
Spectrofluorometer	1

Table continued

Medium-sized laboratory	
Optional items	
High-performance liquid chromatograph detectors:	
— fluorescence	1
— diode-array	1
— refractive index	1
— evaporative light scattering (ELSD)	1
— charged aerosol (CAD)	1
— mass spectrometric (MS)	1
Gas chromatograph detectors:	
— conductivity	1
— nitrogen/phosphorous (NPD)	1
— mass spectrometric (MS)	1
Capillary electrophoresis equipment	1
Thin-layer chromatography scanner	1
Crushing strength tester	1
Friability tester	1
Viscometer	1
Ice machine	1
Solvent-recovery apparatus	1
Equipment for microbiology unit	
pH meter	1
Ultraviolet/visible spectrophotometer, single-beam	1
Microscopes (for bacteriology)	2
Membrane filter assembly for sterility tests	1
Colony counter with magnifier	1
Laminar air flow unit	1
Hot-air sterilizer	1
Incubators, 60 litres	2 or 3
Anaerobic jar	1
Zone reader	1
Centrifuge	1

Table continued

Medium-sized laboratory	
Equipment for microbiology unit	
Water-bath (thermostatically controlled)	2
Autoclaves (100 litres, top-loading)	2
Refrigerators (340 litres)	2
Deep freeze	1
Laboratory glassware washing machine	1
Equipment for pharmacognosy/phytochemistry unit	
Grinder/mill (for preparation of sample of herbal materials)	1
Top loading balance	1
Sieves	1 set
Microscope ^b	1
Soxhlet extraction apparatus	2 or 3
Water-bath	1
Heating mantles for flasks	1 or 2
Hot plates with magnetic stirrers	2
Equipment for thin-layer chromatography	1 or 2
Developing chambers	3 or 4
Desiccators	2
Rotary vacuum apparatus	1
Distillation equipment	1
Conical percolators	2 or 3
Apparatus for determination of water content by azeotropic method ^b	1
Apparatus for determination of volatile oils ^b	1
Apparatus for determination of arsenic limit test ^c	1

^a Needed in the case that herbal medicines are also tested.

^b Quality control methods for medicinal plant materials. Geneva, World Health Organization, 1998.

^c WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues. Geneva, World Health Organization, 2006.

5.2 WHO good practices for pharmaceutical microbiology laboratories

Annex 2, WHO Technical Report Series, 961,
2011

Background

The WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted in 2009 a revised version of the *Good practices for pharmaceutical quality control laboratories* (1).

During the inspections carried out when prequalifying laboratories, the inspectors had noticed that some of the texts of these guidelines might benefit from additional guidance, with a special focus on microbiology.

In light of the above, the Expert Committee recommended that the WHO Secretariat initiate the process of developing a new text on good practices for pharmaceutical microbiology laboratories.

The following text is proposed to cover this specific type of laboratory.

Introduction and scope of document	1154
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2.2 Environmental monitoring in the laboratory	1158
2.3 Cleaning, disinfection and hygiene	1158
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3. Validation of test methods	1160
4. Equipment	1160
4.1 Maintenance of equipment	1161
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4.3 Calibration, performance verification and monitoring of use	1161
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5.1 Reagents	1164
5.2 Media	1164
5.3 Labelling	1165
5.4 Organism resuscitation	1165

6. Reference materials and reference cultures	1166
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Introduction and scope of document

Pharmaceutical microbiology laboratories may be involved in:

- sterility testing;
- detection, isolation, enumeration and identification of microorganisms (bacteria, yeast and moulds) and testing for bacterial endotoxins in different materials (e.g. starting materials, water), products, surfaces, garments and the environment; and
- assay using microorganisms as part of the test system.

These guidelines relate to all microbiology laboratories involved in the above-mentioned testing activities, whether they are independent or a department or unit of a pharmaceutical manufacturing facility.

These guidelines are based on and supplement the requirements described in *Good practices for pharmaceutical quality control laboratories* (1); *General guidelines for the establishment, maintenance and distribution of chemical reference substances. Revision* (2); *The International Pharmacopoeia*, Fourth Edition (3); First Supplement to *The International Pharmacopoeia*, Fourth Edition (4); and ISO/IEC 17025 (5).

Glossary

calibration

The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

certified reference material

Reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by a certificate that provides the value of the specified property, its associated uncertainty and a statement of metrological traceability.

limit of detection

The lowest number of microorganisms that can be detected, but in numbers that cannot be estimated accurately.

precision

The degree of agreement among individual results.

quantitation limit (limit of quantitation)

Applied to quantitative microbiological tests. The lowest number of microorganisms within a defined variability that may be counted under the experimental conditions of the method under evaluation.

reference cultures

Collective term for reference strain and reference stocks.

reference material

Material sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process.

reference method

A method which has been validated as being fit for purpose, with which an alternative method may be compared.

reference stocks

A set of separate identical cultures obtained by a single subculture from the reference strain (6).

reference strains

Microorganisms defined at least to the genus and species level, catalogued and described according to its characteristics and preferably stating its origin (6). Normally obtained from a recognized national or international collection.

repeatability

Closeness of the agreement between the results of successive measurements of the same measure and under the same conditions of measurement (adapted from ISO).

reproducibility

Reproducibility expresses precision between laboratories.

robustness (or ruggedness)

The ability of the procedure to provide analytical results of acceptable accuracy and precision under a variety of conditions.

sensitivity

The fraction of the total number of positive cultures or colonies correctly assigned in the presumptive inspection (7).

specificity (selectivity)

The ability of the method to detect the required range of microorganisms that might be present in the test sample.

validation

Action of proving, in accordance with the principles of good practice quality guidelines and regulations (GxP), that any procedure, process, equipment (including the software or hardware used), material, activity or system actually and consistently leads to the expected results.

verification

The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with GxP principles.

working culture

A primary subculture from a reference stock (6).

1. Personnel

- 1.1 Microbiological testing should be performed and supervised by an experienced person, qualified in microbiology or equivalent. Staff should have basic training in microbiology and relevant practical experience before being allowed to perform work covered by the scope of testing.
- 1.2 Current job descriptions for all personnel involved in tests and/or calibrations, validations and verifications should be maintained. The laboratory should also maintain records of all technical personnel, describing their qualifications, training and experience.
- 1.3 If the laboratory includes opinions and interpretations of test results in reports, this should be done by authorized personnel with suitable experience and relevant knowledge of the specific application including, for example, regulatory and technological requirements and acceptability criteria.
- 1.4 The laboratory management should ensure that all personnel have received adequate training for the competent performance of tests and operation of equipment. This should include training in basic techniques, e.g. plate pouring, counting of colonies, aseptic technique, media preparation, serial dilutions, and basic techniques in identification, with acceptability determined using objective criteria where relevant. Personnel may only perform tests on samples if they are either recognized as competent to do so, or if they do so under adequate supervision. Competence should be monitored continuously with provision for retraining where necessary. Where a method or technique is not in regular use, the competency of the personnel to perform the test should be verified before testing is undertaken. In some cases it is acceptable to relate competence to a general technique or instrument being used rather than to particular methods.

- 1.5 Personnel should be trained in necessary procedures for containment of microorganisms within the laboratory facility.
- 1.6 Personnel should be trained in safe handling of microorganisms.

2. Environment

2.1 Premises

- 2.1.1 Microbiology laboratories and certain support equipment (e.g. autoclaves and glassware) should be dedicated and separated from other areas, especially from production areas.
- 2.1.2 Microbiology laboratories should be designed to suit the operations to be carried out in them. There should be sufficient space for all activities to avoid mix ups, contamination and cross-contamination. There should be adequate suitable space for samples, reference organisms, media (if necessary, with cooling), testing and records. Due to the nature of some materials (e.g. sterile media versus reference organisms or incubated cultures), separate storage locations may be necessary.
- 2.1.3 Laboratories should be appropriately designed and should take into account the suitability of construction materials to enable appropriate cleaning, disinfection and minimize the risks of contamination.
- 2.1.4 There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions, including temperature and humidity controls where required, should be in place for microbiological laboratories. The air supplied to the laboratory should be of appropriate quality and should not be a source of contamination.
- 2.1.5 Access to the microbiological laboratory should be restricted to authorized personnel. Personnel should be made aware of:
 - the appropriate entry and exit procedures including gowning;
 - the intended use of a particular area;
 - the restrictions imposed on working within such areas;
 - the reasons for imposing such restrictions; and
 - the appropriate containment levels.
- 2.1.6 Laboratory activities, such as sample preparation, media and equipment preparation and enumeration of microorganisms, should be segregated by space or at least in time, so as to minimize risks of cross-contamination, false-positive results and false-negative results. Where non-dedicated areas are used,

risk management principles should be applied. Sterility testing should always be performed in a dedicated area.

- 2.1.7 Consideration should be given to designing appropriate classified areas for the operations to be performed within the microbiology laboratory. The classification should be based on the criticality of the product and the operation being carried out in the area. Sterility testing should be performed under the same class as used for sterile/aseptic manufacturing operations. Appendix 1 shows recommendations for zone classifications.
- 2.1.8 In general, laboratory equipment should not routinely be moved between areas of different cleanliness class, to avoid accidental cross-contamination. Laboratory equipment used in the microbiology laboratory should not be used outside the microbiology area, unless there are specific precautions in place to prevent cross-contamination.

2.2 Environmental monitoring in the laboratory

- 2.2.1 Where necessary and appropriate (e.g. in areas for sterility testing) an environmental monitoring programme should be in place which covers, for example, use of active air monitoring, air settling or contact plates, temperature and pressure differentials. Alert and action limits should be defined. Trending of environmental monitoring results should be carried out.

2.3 Cleaning, disinfection and hygiene

- 2.3.1 There should be a documented cleaning and disinfection programme. Results of environmental monitoring should be considered where relevant.
- 2.3.2 There should be a procedure for dealing with spillages.
- 2.3.3 Adequate hand-washing and hand-disinfection facilities should be available.

2.4 Sterility test facilities

- 2.4.1 Sterility test facilities have specific environmental requirements to ensure the integrity of tests carried out. *WHO good manufacturing practices (GMP) for sterile pharmaceutical products* (8) requires that sterility testing should be carried out and specifies requirements for sterility testing. This section details the clean-room requirements for a sterility test facility.
- 2.4.2 Sterility testing should be performed under aseptic conditions, which should be equivalent to air quality standards required for the aseptic manufacture of pharmaceutical products. The premises, services and equipment should be subject to the appropriate qualification process.

- 2.4.3 The sterility testing should be carried out within a Grade A unidirectional airflow protected zone or a biosafety cabinet (if warranted), which should be located within a clean room with a Grade B background. Alternatively, the testing can be carried out within a barrier isolator. Care should be taken with the design of the facility layout and room airflow patterns, to ensure that the unidirectional airflow patterns are not disrupted.
- 2.4.4 The clean-room classification and air-handling equipment of the sterility test facilities should be requalified at least annually by a competent person or contractor. The environment should comply with the non-viable and viable limits, and verification of high efficiency particulate air (HEPA) filter integrity and room airflows should be performed. However, an alternative frequency of the monitoring may be justified based on quality risk management (QRM). Mapping locations for sample points for routine monitoring should be documented, as well as exposure duration, and frequency of all types of microbiological environmental monitoring should be specified in written procedures.
- 2.4.5 Air supplied to Grade A and B zones should be via terminal HEPA filters.
- 2.4.6 Appropriate airflow alarms and pressure differentials and indication instruments should be provided (*GMP: Heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* (8); and *GMP for sterile pharmaceutical products* (8)).
- 2.4.7 Room pressure readings should be taken and recorded from externally mounted gauges unless a validated continuous monitoring system is installed. As a minimum, readings should be taken prior to entry of the operator to the test suite. Pressure gauges should be labelled to indicate the area served and the acceptable specification.
- 2.4.8 Entry to the clean room should be via a system of airlocks and a change room where operators are required to don suitable clean-room garments. The final change room should be under “at rest” conditions of the same grade as the room it serves. Change rooms should be of adequate size for ease of changing. There should be clear demarcation of the different zones.
- 2.4.9 Garments for the sterility test operator should comply with the principles of section 10 of *WHO GMP for sterile pharmaceutical products* (8). Operators should be trained and certified in gowning procedures with training records maintained.
- 2.4.10 The fittings and finishes of the premises should comply with section 11 of *WHO GMP for sterile pharmaceutical products* (8).

2.4.11 Environmental microbiological monitoring should reflect the facility used (room or isolator) and include a combination of air and surface sampling methods appropriate to the facility, such as:

- active air sampling;
- settle (exposure) plates;
- surface contact — replicate organism detection and counting (RODAC) plates, swabs or flexible films;
- operators' glove prints.

Microbial environmental monitoring of the sterility test zone should be performed during every work session under operational (dynamic) conditions.

There should be written specifications, including appropriate alert and action limits for microbial contamination. Limits for microbiological environmental monitoring are given in the *WHO GMP for sterile pharmaceutical products* (8).

3. Validation of test methods

- 3.1 Standard (pharmacopoeial) test methods are considered to be validated. However, the specific test method to be used by a specific laboratory for testing of a specific product needs to be shown to be suitable for use in recovering bacteria, yeast and mould in the presence of the specific product. The laboratory should demonstrate that the performance criteria of the standard test method can be met by the laboratory before introducing the test for routine purposes (method verification) and that the specific test method for the specific product is suitable (test method suitability including positive and negative controls).
- 3.2 Test methods not based on compendial or other recognized references should be validated before use. The validation should comprise, where appropriate, determining accuracy, precision, specificity, limit of detection, limit of quantitation, linearity and robustness. Potentially inhibitory effects from the sample should be taken into account when testing different types of sample. The results should be evaluated with appropriate statistical methods, e.g. as described in the national, regional or international pharmacopoeias.

4. Equipment

Each item of equipment, instrument or other device used for testing, verification and calibration should be uniquely identified.

As part of its quality system, a laboratory should have a documented programme for the qualification, calibration, performance verification, maintenance and a system for monitoring the use of its equipment.

4.1 Maintenance of equipment

- 4.1.1 Maintenance of essential equipment should be carried out at predetermined intervals in accordance with a documented procedure. Detailed records should be kept. (For examples of maintenance of equipment and intervals see Appendix 2.)

4.2 Qualification

- 4.2.1 For qualification of equipment see sections 8 and 12 in *Good practices for pharmaceutical quality control laboratories* (1).

4.3 Calibration, performance verification and monitoring of use

- 4.3.1 The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument.
- 4.3.2 The frequency of calibration and performance verification will be determined by documented experience and will be based on need, type and previous performance of the equipment. Intervals between calibration and verification should be shorter than the time the equipment has been found to take to drift outside acceptable limits. (For examples of calibration checks and intervals for different laboratory equipment, see Appendix 3; and for equipment qualification and monitoring, see Appendix 4.) The performance of the equipment should conform to predefined acceptance criteria.

4.3.3 Temperature measurement devices

- 4.3.3.1 Where temperature has a direct effect on the result of an analysis or is critical for the correct performance of equipment, temperature measuring devices should be of appropriate quality to achieve the accuracy required (e.g. liquid-in-glass thermometers, thermocouples and platinum resistance thermometers (PRTs) used in incubators and autoclaves).
- 4.3.3.2 Calibration of devices should be traceable to national or international standards for temperature.

4.3.4 Incubators, water-baths and ovens

The stability of temperature, uniformity of temperature distribution and time required to achieve equilibrium conditions in incubators, water-baths, ovens and temperature-controlled rooms should be established initially and documented, in particular with respect to typical uses (for example, position, space between, and height of, stacks of Petri dishes). The constancy of the characteristics recorded during initial validation

of the equipment should be checked and recorded after each significant repair or modification. The operating temperature of this type of equipment should be monitored and records retained. The use of the equipment should be considered when determining what temperature controls are required.

4.3.5 Autoclaves, including media preparators

- 4.3.5.1 Autoclaves should be capable of meeting specified time and temperature tolerances; monitoring pressure alone is not acceptable. Sensors used for controlling or monitoring operating cycles require calibration and the performance of timers should be verified.
- 4.3.5.2 Initial validation should include performance studies (spatial temperature distribution surveys) for each operating cycle and each load configuration used in practice. This process must be repeated after any significant repair or modification (e.g. replacement of thermoregulator probe or programmer, change to loading arrangements or operating cycle) or where indicated by the results of quality control checks on media or risk assessment. Sufficient temperature sensors should be positioned within the load (e.g. in containers filled with liquid/medium) to enable location differences to be demonstrated. In the case of media preparators, where uniform heating cannot be demonstrated by other means, the use of two sensors, one adjacent to the control probe and one remote from it, would generally be considered appropriate. Validation and revalidation should consider the suitability of come-up and come-down times as well as time at sterilization temperature.
- 4.3.5.3 Clear operating instructions should be provided based on the heating profiles determined for typical uses during validation/revalidation. Acceptance/rejection criteria should be established and records of autoclave operations, including temperature and time, maintained for every cycle.
- 4.3.5.4 Monitoring may be achieved by one of the following:
- using a thermocouple and recorder to produce a chart or printout;
 - direct observation and recording of maximum temperature achieved and time at that temperature.

In addition to directly monitoring the temperature of an autoclave, the effectiveness of its operation during each cycle may be checked by the use of chemical or biological indicators for sterilization or decontamination purposes. Autoclave tape or indicator strips should be used only to show that a load has been processed, not to demonstrate completion of an acceptable cycle.

Laboratories should have a separate autoclave for decontamination. However, in exceptional cases one autoclave may be acceptable provided that extensive precautions are taken to separate decontamination and sterilization loads, and a documented cleaning programme is in place to address both the internal and external environment of the autoclave.

4.3.6 Weights and balances

Weights and balances shall be calibrated traceably at regular intervals (according to their intended use) using appropriate standard weights traceable to certified standard weights.

4.3.7 Volumetric equipment

- 4.3.7.1 Microbiology laboratories should carry out initial verification of volumetric equipment (automatic dispensers, dispenser/diluters, mechanical hand pipettes and disposable pipettes) and then make regular checks, as appropriate, to ensure that the equipment is performing within the required specification. Initial verification should not be necessary for glassware which has been certified to a specific tolerance. Equipment should be checked for the accuracy of the delivered volume against the set volume (for several different settings in the case of variable volume instruments) and the precision of the repeat deliveries should be measured.
- 4.3.7.2 For “single-use” disposable volumetric equipment, laboratories should obtain supplies from companies with a recognized and relevant quality system. After initial validation of the suitability of the equipment, it is recommended that random checks on accuracy are carried out. If the supplier does not have a recognized quality system, laboratories should check each batch of equipment for suitability.

4.3.8 Other equipment

Conductivity meters, oxygen meters, pH meters and other similar instruments should be verified regularly or before each use. The buffers used for verification purposes should be stored in appropriate conditions and should be marked with an expiry date.

Where humidity is important to the outcome of the test, hygrometers should be calibrated, the calibration being traceable to national or international standards.

Timers, including the autoclave timer, should be verified using a calibrated timer or national time signal.

When centrifuges are used in test procedures, an assessment of the rotations per minute (RPM) should be made. Where it is critical, the centrifuge should be calibrated.

5. Reagents and culture media

Laboratories should ensure that the quality of reagents and media used is appropriate for the test concerned.

5.1 Reagents

5.1.1 Laboratories should verify the suitability of each batch of reagents critical for the test, initially and during its shelf-life.

5.2 Media

5.2.1 Media may be prepared in-house or purchased either partially or fully prepared. Vendors of purchased media should be approved and qualified. The qualified vendor may certify some of the quality parameters listed subsequently. Growth promotion and, if appropriate, other suitable performance tests (see section 5.2.2) should be done on all media on every batch and on every shipment. Where the supplier of fully prepared media is qualified and provides growth promotion certification per batch of media and transportation conditions have been qualified, the user may rely on the manufacturer's certificate with periodic verification of his or her results.

5.2.2 The suitable performance of culture media, diluents and other suspension fluids should be checked, where relevant, with regard to:

- recovery or survival maintenance of target organisms. Recovery of 50–200% (after inoculation of not more than 100 colony-forming units (CFU or cfu) should be demonstrated;
- inhibition or suppression of non-target organisms;
- biochemical (differential and diagnostic) properties; and
- other appropriate properties (e.g. pH, volume and sterility).

Quantitative procedures for evaluation of recovery or survival are preferred.

5.2.3 Raw materials (both commercial dehydrated formulations and individual constituents) and media should be stored under appropriate conditions recommended by the manufacturer, e.g. cool, dry and dark. All containers, especially those for dehydrated media, should be sealed tightly. Dehydrated media that are caked or cracked or show a colour change should not be used.

5.2.4 Water of a suitable microbiological quality and which is free from bactericidal, inhibitory or interfering substances, should be used for preparation unless the test method specifies otherwise.

- 5.2.5 Media containing antimetabolites or inhibitors should be prepared using dedicated glassware, as carry-over of these agents into other media could inhibit the growth and detection of microorganisms present in the sample under test. If dedicated glassware is not used, washing procedures for glassware should be validated.
- 5.2.6 Repartition of media after sterilization should be performed under unidirectional airflow (UDAF) to minimize potential for environmental contamination. This should be considered a minimum requirement for media to be used in relation to sterile product testing. This includes the cooling of media, as container lids will need to be removed during cooling to prevent build-up of condensation.
- 5.2.7 Plated media which is to be irradiated may require the addition of an antioxidant and free radical scavenger to provide protection from the effects of the irradiation process. The irradiated media should be validated by performing quantitative growth promotion testing on both irradiated and non-irradiated media.
- 5.2.8 Shelf-life of prepared media under defined storage conditions shall be determined and verified.
- 5.2.9 Batches of media should be identifiable and their conformance with quality specifications documented. For purchased media the user laboratory should ensure that it will be notified by the manufacturer of any changes to the quality specification.
- 5.2.10 Media should be prepared in accordance with any manufacturer's instructions, taking into careful account specifications such as time and temperature for sterilization.
- 5.2.11 Microwave devices should not be used for the melting of media due to the inconsistent distribution of the heating process.

5.3 Labelling

- 5.3.1 Laboratories should ensure that all reagents (including stock solutions), media, diluents and other suspending fluids are adequately labelled to indicate, as appropriate, identity, concentration, storage conditions, preparation date, validated expiry date and/or recommended storage periods. The person responsible for preparation should be identifiable from records.

5.4 Organism resuscitation

- 5.4.1 Organism resuscitation is required where test methodologies may produce sublethally injured cells. For example, exposure to:

- injurious effects of processing, e.g. heat;
- antimicrobial agents;
- preservatives;
- extremes of osmotic pressure; and
- extremes of pH.

5.4.2 Organism resuscitation may be achieved by:

- exposure to a liquid media like a simple salt solution at room temperature for 2 hours;
- exposure to a solid repair medium for 4–6 hours.

6. Reference materials and reference cultures

6.1 International standards and pharmacopoeial reference substances

6.1.1 Reference materials and certified reference materials are generally used in a microbiological laboratory to qualify, verify and calibrate equipment.

Whenever possible these reference materials should be used in appropriate matrices.

International standards and pharmacopoeial reference substances are employed, for example, to:

- determine potency or content;
- validate methods;
- enable comparison of methods;
- perform positive controls; and
- perform growth promotion tests.

If possible reference materials should be used in appropriate matrices.

6.2 Reference cultures

6.2.1 Reference cultures are required for establishing acceptable performance of media (including test kits), for validating methods, for verifying the suitability of test methods and for assessing or evaluating ongoing performance. Traceability is necessary, for example, when establishing media performance for test kit and method validations. To demonstrate traceability, laboratories must use reference strains of microorganisms obtained directly from a recognized national or

international collection, where these exist. Alternatively, commercial derivatives for which all relevant properties have been shown by the laboratory to be equivalent at the point of use may be used.

- 6.2.2 Reference strains may be subcultured once to provide reference stocks. Purity and biochemical checks should be made in parallel as appropriate. It is recommended to store reference stocks in aliquots either deep-frozen or lyophilized. Working cultures for routine use should be primary subcultures from the reference stock (see Appendix 5 on general use of reference cultures). If reference stocks have been thawed, they must not be refrozen and reused.
- 6.2.3 Working stocks should not normally be subcultured. Usually not more than five generations (or passages) from the original reference strain can be subcultured if defined by a standard method or laboratories can provide documentary evidence that there has been no change in any relevant property. Commercial derivatives of reference strains may only be used as working cultures.

7. Sampling

For general principles reference is made to *Good practices for pharmaceutical quality control laboratories* (1).

- 7.1 Where testing laboratories are responsible for primary sampling to obtain test items, it is strongly recommended that this sampling be covered by a quality assurance system and it should be subject to regular audits.
- 7.2 Any disinfection processes used in obtaining the sample (e.g. disinfection of sample points) should not compromise the microbial level within the sample.
- 7.3 Transport and storage of samples should be under conditions that maintain the integrity of the sample (e.g. chilled or frozen where appropriate). Testing of the samples should be performed as soon as possible after sampling. For samples where a growth in the microbial population during transport and storage is possible it should be demonstrated that the storage conditions, time and temperature, will not affect the accuracy of the testing result. The storage conditions should be monitored and records kept. The responsibility for transport, storage between sampling and arrival at the testing laboratory should be clearly documented.
- 7.4 Sampling should only be performed by trained personnel. It should be carried out aseptically using sterile equipment. Appropriate precautions should be taken to ensure that sample integrity is maintained through the use of sterile sealed containers for the collection of samples where appropriate. It may be necessary to monitor environmental conditions, for example, air contamination and temperature, at the sampling site. Time of sampling should be recorded, if appropriate.

8. Sample handling and identification

- 8.1 The laboratory should have procedures that cover the delivery and receipt of samples and sample identification. If there is insufficient sample or the sample is in poor condition due to physical deterioration, incorrect temperature, torn packaging or deficient labelling, the laboratory should consult with the client before deciding whether to test or refuse the sample.
- 8.2 The laboratory should record all relevant information, e.g.
 - date and, where relevant, the time of receipt;
 - condition of the sample on receipt and, when necessary, temperature; and
 - characteristics of the sampling operation (including sampling date and sampling conditions).
- 8.3 Samples awaiting testing should be stored under suitable conditions to minimize changes to any microbial population present. Storage conditions should be validated, defined and recorded.
- 8.4 The packaging and labels of samples may be highly contaminated and should be handled and stored with care so as to avoid any spread of contamination. Disinfection processes applied to the outer container should not affect the integrity of the sample. It should be noted that alcohol is not sporicidal.
- 8.5 Subsampling by the laboratory immediately prior to testing may be required as part of the test method. It may be appropriate that it is performed according to national or international standards, where they exist, or by validated in-house methods. Subsampling procedures should be designed to collect a representative sample.
- 8.6 There should be a written procedure for the retention and disposal of samples. If sample integrity can be maintained it may be appropriate that samples are stored until the test results are obtained, or longer if required. Laboratory sample portions that are known to be contaminated should be decontaminated prior to being discarded (see section 11.1).

9. Disposal of contaminated waste

- 9.1 The procedures for the disposal of contaminated materials should be designed to minimize the possibility of contaminating the test environment or materials. It is a matter of good laboratory management and should conform to national/international environmental or health and safety regulations.

10. Quality assurance of results and quality control of performance

10.1 Internal quality control

10.1.1 The laboratory should have a system of internal quality assurance or quality control (e.g. handling deviations, use of spiked samples, replicate testing and participation in proficiency testing, where appropriate) to ensure the consistency of results from day to day and their conformity with defined criteria.

11. Testing procedures

- 11.1 Testing should normally be performed according to procedures described in the national, regional and international pharmacopoeias.
- 11.2 Alternative testing procedures may be used if they are appropriately validated and equivalence to official methods has been demonstrated.

12. Test reports

- 12.1 If the result of the enumeration is negative, it should be reported as “not detected for a defined unit” or “less than the detection limit for a defined unit”. The result should not be given as “zero for a defined unit” unless it is a regulatory requirement. Qualitative test results should be reported as “detected/not detected in a defined quantity or volume”. They may also be expressed as “less than a specified number of organisms for a defined unit” where the specified number of organisms exceeds the detection limit of the method and this has been agreed with the client. In the raw data the result should not be given as zero for a defined unit unless it is a regulatory requirement. A reported value of “0” may be used for data entry and calculations or trend analysis in electronic databases
- 12.2 Where an estimate of the uncertainty of the test result is expressed on the test report, any limitations (particularly if the estimate does not include the component contributed by the distribution of microorganisms within the sample) have to be made clear to the client.

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Further reading

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- ISO 6887-1 (1999) *Microbiology of food and animal feeding stuffs — Preparation of test samples, initial suspension and decimal dilutions for microbiological examination — Part 1: General rules for the preparation of the initial suspension and decimal dilutions*.
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- Draft ISO/FDIS (2003) 11133-2. *Microbiology of food and animal feeding stuffs. Guidelines on preparation and production of culture media. Part 2 — Practical guidelines on performance testing on culture media*.
- EN 12741 (1999). *Biotechnology — Laboratories for research, development and analysis — Guidance for biotechnology laboratory operations*.

Appendix 1

Examples of zones in which operations could be carried out

The zones are designed as the following grades, during the installation and monitoring can be carried out, e.g. through appropriate air supply.

Zone	Installation grade	Proposed
Sample receipt	Unclassified	Unclassified
Media preparation	Unclassified	Unclassified
Autoclave loading	Unclassified	Unclassified
Autoclave unloading, inside the sterility testing area	Grade B	ISO 5 (turbulent) and <10 cfu/m ³
Sterility testing — UDAF	Grade A	ISO 5 (UDAF) and <1 cfu/m ³
Sterility testing — background to UDAF	Grade B	ISO 5 (turbulent) and <10 cfu/m ³
Sterility testing — isolator	Grade A (NVP and microbiology only)	ISO 5 (UDAF) and <1 cfu/m ³
Sterility testing — background to isolator	Unclassified	Unclassified
Incubator	Unclassified	Unclassified
Enumeration	Unclassified ^a	Unclassified ^a
Decontamination	Unclassified	Unclassified

cfu, colony-forming unit.

^a Critical steps should be done under laminar flow.

Appendix 2

Examples of maintenance of equipment

This information is provided as an example and the frequency will be based on the need, type and previous performance of the equipment and on the recommendations in suppliers' manuals.

Type of equipment	Requirement	Suggested frequency
– Incubators – Fridges – Freezers, ovens	Clean and disinfect internal surfaces	– Monthly – When required (e.g. every 3 months) – When required (e.g. annually)
Water-baths	Empty, clean, disinfect and refill	– Monthly, or every 6 months if biocide used
Centrifuges	– Service – Clean and disinfect	– Annually – Each use
Autoclaves	– Make visual checks of gasket, clean/drain chamber – Full service – Safety check of pressure vessel	– Regularly, as recommended by manufacturer – Annually or as recommended by manufacturer – Annually
Safety cabinets unidirectional cabinets	Full service and mechanical check	Annually or as recommended by manufacturer
Microscopes	Full maintenance service	Annually
pH meters	Clean electrode	Each use
Balances, gravimetric diluters	– Clean – Service	– Each use – Annually
Stills	Clean and descale	As required (e.g. every 3 months)
De-ionizers, reverse osmosis units	Replace cartridge/membrane	As recommended by manufacturer
Anaerobic jars	Clean/disinfect	After each use
Media dispensers, volumetric equipment, pipettes and general service equipment	Decontaminate, clean and sterilize as appropriate	Each use

Table continued

Type of equipment	Requirement	Suggested frequency
Spiral platers	<ul style="list-style-type: none"> – Service – Decontaminate, clean and sterilize 	<ul style="list-style-type: none"> – Annually – Each use
Laboratory	<ul style="list-style-type: none"> – Clean and disinfect working surfaces – Clean floors, disinfect sinks and basins – Clean and disinfect other surfaces 	<ul style="list-style-type: none"> – Daily and during use – Daily – Every 3 months

Appendix 3

Examples of calibration checks and intervals for different laboratory equipment

This information is provided as an example and the frequency will be based on the need, type, previous performance and criticality of the equipment.

Type of equipment	Requirement	Suggested frequency
Reference thermometers (liquid-in-glass)	Full traceable recalibration Single point (e.g. ice-point check)	Every 3 years Annually
Reference thermocouples	Full traceable recalibration Check against reference thermometer	Every 3 years Annually
Working thermometers and working thermocouples	Check against reference thermometer at ice-point and/or working temperature range	Annually
Balances	Full traceable calibration	Annually
Calibration weights	Full traceable calibration	Annually
Check weight(s)	Check against calibrated weight or check on balance immediately following traceable calibration	Annually
Volumetric glassware	Gravimetric calibration to required tolerance	Annually
Microscopes	Traceable calibration of stage micrometer (where appropriate)	Initially
Hygrometers	Traceable calibration	Annually
Centrifuges	Traceable calibration or check against an independent tachometer, as appropriate	Annually

Appendix 4

Examples of equipment qualification and monitoring

This information is provided as an example and the frequency will be based on the need, type, previous performance and criticality of the equipment.

Type of equipment	Requirement	Suggested frequency
Temperature-controlled equipment (incubators, baths, fridges, freezers)	<ul style="list-style-type: none"> – Establish stability and uniformity of temperature – Monitor temperature 	<ul style="list-style-type: none"> – Initially, every 2 years and after repair/modification – Daily/each use
Sterilizing ovens	<ul style="list-style-type: none"> – Establish stability and uniformity of temperature – Monitor temperature 	<ul style="list-style-type: none"> – Initially, every 2 years and after repair/modification – Each use
Autoclaves	<ul style="list-style-type: none"> – Establish characteristics for loads/cycles – Monitor temperature/pressure/time 	<ul style="list-style-type: none"> – Initially, every 2 years and after repair/modification – Each use
Grade A areas used for sterility testing: • safety unidirectional cabinets • isolators	<ul style="list-style-type: none"> – Establish performance – Microbiological monitoring – Airflow monitoring – Test for integrity of HEPA filters 	<ul style="list-style-type: none"> – Initially, every year and after repair/modification – Each use – 6-monthly – 6-monthly
Unidirectional cabinets	<ul style="list-style-type: none"> – Establish performance – Microbiological monitoring – Airflow monitoring – Test for integrity of HEPA filters 	<ul style="list-style-type: none"> – Initially, and after repair/modification – Weekly – 6-monthly – 6-monthly
Timers	Check against national time signal	– Annually
Microscopes	Check alignment	Daily/each use
pH meters	Adjust using at least two buffers of suitable quality	Daily/each use
Balances	Check zero, and reading against check weight	Daily/each use

Table continued

Type of equipment	frequency and nature of use)	Suggested frequency
De-ionizers and reverse osmosis units	<ul style="list-style-type: none"> – Check conductivity – Check for microbial contamination 	<ul style="list-style-type: none"> – Weekly – Monthly
Gravimetric diluters	<ul style="list-style-type: none"> – Check weight of volume dispensed – Check dilution ratio 	<ul style="list-style-type: none"> – Daily – Daily
Media dispensers	Check volume dispensed	Each adjustment or replacement
Pipettors/pipettes	Check accuracy and precision of volume dispensed	Regularly (to be defined by taking account of the frequency and nature of use)
Spiral platers	<ul style="list-style-type: none"> – Establish performance against conventional method – Check stylus condition and the art start and end-points – Check volume dispensed 	<ul style="list-style-type: none"> – Initially and annually – Daily/each use – Monthly
Colony counters	Check against number counted manually	Annually
Centrifuges	Check speed against a calibrated and independent tachometer	Annually
Anaerobic jars/ incubators	Check with anaerobic indicator	Each use
Laboratory environment	Monitor for airborne and surface microbial contamination using, e.g. air samplers, settle plates, contact plates or swabs	Based on risk assessment, an appropriate environmental monitoring programme should be established

HEPA, high-efficiency particulate air.

Appendix 5

General use of reference cultures

Reference strain

from source recognized by accreditation body



Reference stock G1

Freeze-dried, liquid nitrogen storage, deep frozen, etc.
Specified conditions and recommended storage times



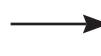
Working culture

Specified conditions and
recommended storage times
Routine use



Reference stock G2

Freeze-dried, liquid nitrogen storage, deep frozen, etc.
Specified conditions and recommended storage times



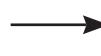
Working culture

Specified conditions and
recommended storage times
Routine use



Reference stock G3

Freeze dried, liquid nitrogen storage, deep frozen, etc.
Specified conditions and recommended storage times



Working culture

Specified conditions and
recommended storage times
Routine use



Reference stock G4

Freeze-dried, liquid nitrogen storage, deep frozen, etc.
Specified conditions and recommended storage times



Working culture

Specified conditions and
recommended storage times
Routine use



Working culture

Specified conditions and recommended storage times
Routine use

All parts of the process should be fully documented and detailed records of all stages must be maintained. Purity checks and biochemical tests should be made as appropriate.

5.3 Good chromatography practices

Annex 4, WHO Technical Report Series, 1025,
2020 (new)

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1. Introduction and scope

- 1.1 The use of chromatography methods such as high-performance liquid chromatography, also referred to as high-pressure liquid chromatography (HPLC), and gas chromatography (GC) in quality control laboratory analysis has increased significantly in recent years. Observations during inspections have shown that there was a need for a specific good practices (GXP) document.
- 1.2 HPLC and GC methods are used in, for example, the identification of materials and products, for determination of assay and related substances in materials and products, as well as in validation such as process validation and cleaning validation. *Note:* Although thin-layer chromatography methods are also used, this approach is not specifically addressed in detail in this document.
- 1.3 Owing to the criticality of the results obtained through chromatography, it must be ensured that the data acquired meet ALCOA+ principles (i.e. attributable, legible, contemporaneous, original and accurate, with additional emphases [see Glossary]).
- 1.5 This document provides information on GXP to be considered in the analysis of samples when chromatographic methods and systems are used. The principles should be applied in the analysis of, for example, raw materials, starting materials, intermediates, in-process materials and finished products.
- 1.6 The principles contained in this guideline are applicable to general chromatographic analysis used in, for example, assay determination, testing for related substances and impurities, process validation, cleaning validation, cleaning verification and stability testing.

2. Glossary

The definitions given below apply to the terms used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts. Note: For general definitions relating to chromatography, see the relevant pharmacopoeia recognized by the national medicines regulatory authority.

ALCOA. A commonly used acronym for “attributable, legible, contemporaneous, original and accurate”.

ALCOA+. A commonly used acronym for “attributable, legible, contemporaneous, original and accurate” that puts additional emphasis on the attributes of being complete, consistent, enduring and available – implicit basic ALCOA principles.

audit trail. A form of metadata that contains information associated with actions that relate to the creation, modification or deletion of GXP records. An audit trail provides for

secure recording of life-cycle details such as creation, additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or overwriting the original record. An audit trail facilitates reconstruction of the history of such events relating to the record, regardless of its medium, including the “who, what, when and why” of the action.

back-up. A copy of one or more electronic files created as an alternative in case the original data or system are lost or become unusable (for example, in the event of a system crash or corruption of a disk). It is important to note that back-up differs from archival, in that back-up copies of electronic records are typically only temporarily stored for the purposes of disaster recovery and may be periodically overwritten. Such temporary back-up copies should not be relied upon as an archival mechanism.

calibration. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

data. All original records and true copies of original records, including source data and metadata and all subsequent transformations and reports of these data, that are generated or recorded at the time of the good manufacturing practices (GMP) activity and allow full and complete reconstruction and evaluation of the GMP activity. Data should be accurately recorded by permanent means at the time of the activity. Data may be contained in paper records (such as worksheets and logbooks), electronic records and audit trails, photographs, microfilm or microfiche, audio- or video-files, or any other media whereby information related to GMP activities is recorded.

data integrity. The degree to which data are complete, consistent, accurate, trustworthy and reliable and to which these characteristics of the data are maintained throughout the data life-cycle. The data should be collected and maintained in a secure manner, such that they are attributable, legible, contemporaneously recorded, original or a true copy and accurate. Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices.

metadata. Data about data that provide the contextual information required to understand those data. Metadata necessary to evaluate the meaning of data should be securely linked to the data and subject to adequate review. Examples of metadata include the time/date stamp of an activity, the operator identification (ID) of the person who performed an activity, the instrument ID used, processing parameters, sequence files, audit trails and other data required to understand data and reconstruct activities.

qualification. Documented evidence that premises, systems or equipment are able to achieve the predetermined specifications, are properly installed, and/or work correctly, and lead to the expected results.

sample set. The combination of samples, standards and blanks prepared for analysis, which includes the specified sequence to be injected or analysed.

source data. Original data obtained as the first-capture of information, whether recorded on paper or electronically.

validation. The action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.

3. Chromatographic systems

- 3.1 Chromatographic systems should meet regulatory and GXP requirements. This should include, for example, ensuring that data are acquired, processed and stored in accordance with ALCOA+ principles (see Glossary).
- 3.2 Supplier selection and vendor qualification should ensure that hardware and software are suitable for their intended application.
- 3.3 Valid agreements should specify the respective responsibilities between the purchaser and supplier and include arrangements for after-sales services.
- 3.4 Chromatographic systems selected, installed and qualified should be appropriate for their intended use.
- 3.5 The environment in which such systems are placed should be appropriate to support their performance. This may include, for example, control of temperature and relative humidity in the area.

4. Qualification, validation, maintenance and calibration

- 4.1 The scope and the extent of validation and qualification of chromatographic systems should be determined based on risk management principles. This includes hardware and software.
- 4.2 The approach to, and execution of, validation and qualification should be described in an authorized document such as a validation master plan.
- 4.3 All stages of qualification should be considered and may include, for example, user requirement specifications (URS), design qualification (DQ), factory acceptance

test (FAT), site acceptance test (SAT), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

- 4.4 Validation and qualification should be described in protocols and recorded in reports. Reports should contain documented evidence and include, for example, screenshots, printouts or other source data and metadata of tests executed as part of validation and qualification.
- 4.5 The data should provide evidence of the consistency of performance of the system and reliable and accurate results.
- 4.6 Parameters such as, but not limited to, password control, audit trail, access and privileges should be described and verified during validation and qualification.
- 4.7 Maintenance, preventive maintenance and calibration of chromatographic systems should be done in accordance with written procedures. Records should be maintained.
- 4.8 Root cause analysis, impact assessment and risk assessment should be done when any calibration parameter is found to be out of calibration or not meeting the predefined limits. Appropriate corrective and preventive action should be taken and documented.

5. Access and privileges

- 5.1 There should be a standard operating procedure (SOP) for the creation and deletion of user groups and users of the chromatographic system, indicating the relevant privileges allocated to each user. Records should be maintained.
- 5.2 An up-to-date record of user groups and users should be maintained.
- 5.3 Users in each group should be appropriately qualified for the responsibility and privileges allocated.
- 5.4 Where required, justification should be provided for privileges granted to user groups or users, including all exceptions.
- 5.5 User privileges reflected in written procedures should be a true reflection of the privileges allocated electronically.
- 5.6 Administrator access rights should not be given to other users on the system.

6. Audit trail

- 6.1 Chromatographic systems should have an audit trail(s) which reflect(s), for example, users, dates, times, original data and results, changes and reasons for change.
- 6.2 Full audit trails should be enabled from the time of installation of software.
- 6.1. Audit trails should remain enabled throughout the life-cycle of a chromatographic system.
- 6.3 Audit trails should be reviewed in accordance with an SOP and include systems and project audit trails. There should be evidence of regular review of an audit trail (for example, each sample sequence or sample set in chromatographic analysis) and of periodic review of audit trails. (Periodic review should be done at specified intervals, based on risk management principles.)
- 6.4 Audit trails are part of metadata and should be stored as part of the data set for all chromatographic analyses.

7. Date and time functions

- 7.1 Chromatographic systems should have date and time functions enabled from the time of installation of the software.
- 7.2 The date and time function should be locked, and access to change the date and time should be controlled. (This includes changes to time zone setting.)
- 7.3 All GMP actions on chromatographic systems should be date- and time-tracked.

8. Electronic systems

Note: This includes computerized systems.

- 8.1 Written procedures should be followed when a new electronic system is taken into use. Procedures should also be followed for the removal of a system from use. Records should be maintained.
- 8.2 Software selected, installed and applied for acquisition, processing and calculation of results should be suitable for its intended use, validated, and render results meeting regulatory, GXP and ALCOA+ principles.
- 8.3 It is preferable that all chromatographic systems be linked to a network system where data are stored and managed on a centralized server.

- 8.4 Stand-alone systems should be appropriately managed. Risk assessment should be done to ensure that sufficient controls are in place to eliminate the risks associated with stand-alone systems. These include, but are not limited to, access, privileges, date and time function, audit trail, data back-up and data management.
- 8.1. Electronic data management systems (EDMS) should be considered for the appropriate management of data, including acquisition, processing and storage of data. EDMS should be appropriate for their intended use and ensure the accuracy and reliability of data acquired and processed.

9. Solvents, buffer solutions and mobile phases

- 9.1 Solvents, buffer solutions and mobile phases should be prepared, stored and used in accordance with authorized specifications and procedures and a relevant pharmacopoeia recognized by the national medicines regulatory authority. These should be used within appropriate, scientifically justifiable timelines.
- 9.2 Records for their preparation and use should be maintained.
- 9.3 Chemicals, reagents and other materials used should be of appropriate grade and quality.
- 9.4 Liquid mobile phases should be filtered, degassed and pressurized when required.
- 9.5 Carrier gases used for gas chromatography should have the appropriate purity and be suitable for their intended use.

10. Column management

- 10.1 Columns used in chromatography should be appropriate for their intended use.
- 10.2 Columns should be purchased from approved suppliers.
- 10.3 Columns should be verified on initial receipt and checked for their suitability as part of the chromatographic system, prior to use in analysis.
- 10.4 Tubing and fittings should be appropriate to ensure that the system performs as expected.
- 10.5 The number of theoretical plates (column efficiency) should be monitored to ensure efficiency is obtained for acceptable chromatography.
- 10.6 Columns should be equilibrated before the analysis. The column oven (and column) temperature should be controlled when specified in the analytical procedure.

- 10.7 The required flow rate should be specified in relevant test procedures. It should be appropriate for the column to be used, to ensure optimal chromatographic separation without exceeding recommended maximum backpressure.
- 10.8 The use of columns should be recorded in a traceable manner. This includes, for example, the unique column identification number, number of injections and washing of the column.
- 10.9 Columns should be washed (cleaned or flushed) according to defined procedures describing the steps and parameters, such as sequence, temperature, flow rate and time.
- 10.10 Columns should be stored in a manner that ensures that they are not damaged.

11. Sample management and sample set

Note: Inappropriate management of samples may result in errors during analysis. Written procedures should be followed to avoid such risks.

- 11.1 Sample management in the laboratory (including the receipt and preparation of samples) should be considered an important aspect in good chromatography practices.
- 11.2 Samples received for analysis should be entered in an appropriate record that ensures the traceability of the sample detail and analysis.
- 11.3 Samples should be stored under appropriate conditions.
- 11.4 Samples (as well as blank and standard solutions) should be prepared in accordance with the authorized specifications and standard test procedures. Records for the preparation should be maintained.
- 11.5 Official, secondary or working standards used should be traceable to the records maintained for their purchase, preparation and storage.
- 11.6 Standard and sample solutions prepared for use in chromatography should be used within defined timelines derived from analytical procedure validation and stability data, as appropriate.
- 11.7 The sample set should be defined. The vials with standard solution(s), sample solution(s) and blank solution(s) should be verified to ensure the correct sequence of injections in the chromatographic system before starting the sequence of injections.
- 11.8 Where carry-over or interference in analysis is relevant, suitable precautions should be taken, such as the inclusion of a blank in the sequence of injections.

- 11.9 The use of “trial injections”, “system check injections”, or other injections that are not specified as part of a sample set, is not recommended. In exceptional cases where this is done, authorized procedures should clearly describe this approach. (Normally, only standard solutions may be used for this purpose, unless otherwise needed and justified e.g. biologics). The electronic record of results in such cases should be saved and stored, together with the results of the sample set for analysis.
- 11.10 A system suitability test (SST) should be part of the sample set. The SST should be performed as described in the respective pharmacopoeia monograph or validated in-house specification and standard test procedure. The SST should meet the predefined acceptance criteria, before samples are injected and throughout the analysis.
- 11.11 Acceptance criteria should be set for the SST, bracketing standards, deviation from relative retention and any other aspect that may be deemed necessary for the chromatographic analysis. This includes acceptability of peak shapes.
- 11.12 Bracketing standards (standard solution injections) should be included in the sample set, at defined intervals, where appropriate. The number of bracketing standards included in a sample set should be defined. Compliance with the defined acceptance criteria should be verified.
- 11.13 Where blank interferences are detected, these should be within predefined limits.

12. Chromatographic methods (acquisition and processing)

- 12.1 Chromatographic methods should be suitable for their intended use. Appropriate acceptance criteria should be specified for parameters such as selectivity (resolution and/or peak-to-valley ratio), sensitivity (signal-to-noise ratio), peak symmetry, repeatability and integration conditions (if applicable).
- 12.2 Where non-pharmacopoeia methods are to be used, these should be developed, validated and described in detail in standard procedures. These procedures should be followed by qualified, trained, experienced personnel.
- 12.3 It is preferable that methods are created and saved in the chromatographic system by authorized personnel. The method selected for analysis from the saved methods should not be modified, unless approved for the intended purpose by authorized personnel.
- 12.4 Data acquisition and processing software should be appropriately validated or verified as being suitable for use. Methods selected for acquisition and processing should be traceable and reflected in the audit trail.

- 12.5 Methods should be proven to remain in a validated state throughout their life-cycle.
- 12.6 Chromatographic conditions (such as the composition of the mobile phase, pH, column dimensions) may be adjusted, within specified limits and in accordance with written procedures, to obtain the separation required. The adjustments made should be within the limits specified (such as defined in the design space of the analytical procedure). The SST requirements (e.g. resolution, symmetry, repeatability) should be met, and retention times and relative retention should be similar.

13. Peak integration

- 13.1 Peak areas in chromatograms should be accurately and consistently integrated in a scientifically sound manner.
- 13.2 Where possible, HPLC and GC instruments should be interfaced with computerized chromatographic data-capturing and processing systems that are capable of applying the integration parameters set, automatically and consistently.
- 13.3 To facilitate the accurate integration of chromatographic peaks, it is preferable that all of the peaks are fully separated. However, when quantitative data are to be obtained from unresolved peaks, the laboratory should have clear policies as to how such peaks should be integrated. This should include a description of the type of integration to be used, with a justification for its use, including, for example:
- tangential skim;
 - exponential skim;
 - exponential curve fitting;
 - straight line skim;
 - front peak skim;
 - rear peak skim;
 - peak-to-valley ratio; and
 - valley height ratio.
- 13.4 Validated methods, specified chromatographic conditions and good chromatography practices should facilitate obtaining symmetrical peaks. Where atypical peak shapes are observed, these should be investigated and appropriate action taken.
- 13.5 Where manual integration has to be done, authorized procedures should be followed. Records should be maintained and include the authorization and justification for manual integration.

- 13.6 Using a procedure to integrate peak height or area by manually setting the baseline using chromatographic software should only be allowed in exceptional cases. Only trained, experienced users should be granted privileges to do so. Records and justification should be given when this procedure is followed.
- 13.7 Where smoothing is applied, the type of “filter” used and the extent of smoothing should be justified.

14. Data management

- 14.1 Chromatographic data should be managed in accordance with this guideline and other related guidelines (1–3).
- 14.2 Procedures should be followed for timely processing and review of data and reporting of results.
- 14.3 Data should be backed up according to procedures, and records maintained as proof thereof. Special care should be taken to ensure frequent back-up of data from stand-alone systems, to prevent loss of data.
- 14.4 Data should be safely stored in a way that includes control over access to data. Backed-up data should be stored at a separate location. Some data should be randomly selected for restoration and verification, at defined intervals, in accordance with a written procedure.
- 14.5 Where appropriate, paper printed records (including data and metadata) may be retained as part of the analytical report reflecting analyses performed.
- 14.6 Procedures should be in place to allow for recovery of chromatographic data in case of disasters such as instrument failure, viruses, hardware or software failure and power failure.
- 14.7 Complete data should be retained for appropriate periods of time, to allow for data verification, inspection, registration or other reasons.

Note: See other guidelines addressing computerized systems (1), data integrity (2) and good documentation practices (3).

References

1. Good manufacturing practices: guidelines on validation. Appendix 5. Validation of computerized systems. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; <https://iris.who.int/bitstream/handle/10665/312316/9789241210287-eng.pdf?sequence=1&isAllowed=y>, accessed 29 January 2020).
2. Guideline on data integrity. Draft for comments. Geneva: World Health Organization; 2019 (Working document QAS/19.819).
3. Guidance on good data and record management practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 5 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>, accessed 4 November 2019).

Further reading

- The International Pharmacopoeia, 9th ed. Geneva: World Health Organization; 2019 (<https://apps.who.int/phint/en/p/docf/>, accessed 4 November 2019).
- European pharmacopoeia (Ph. Eur.), 9th edition. Strasbourg: Council of Europe; 2019.
- United States Pharmacopoeia (<https://www.usp.org/>, accessed 5 December 2019).
- Good manufacturing practices: guidelines on validation. Appendix 6. Guidelines on qualification. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (<https://iris.who.int/bitstream/handle/10665/312316/9789241210287-eng.pdf?sequence=1&isAllowed=y>, accessed 29 January 2020).
- WHO good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957; https://iris.who.int/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1&isAllowed=y, accessed 5 December 2019).

5.4 WHO guidelines for preparing a laboratory information file

Annex 13, WHO Technical Report Series, 961, 2011

Background

The WHO Expert Committee on Specifications for Pharmaceutical Preparations adopted in its thirty-eighth report in 2003 the *Guidelines for preparing a laboratory information file* (WHO Technical Report Series, No. 917, 2003, Annex 5).

The content of these guidelines is closely related to *WHO guidelines on good practices for pharmaceutical quality control laboratories*, which have recently been revised (the revised version was adopted by the WHO Expert Committee at its forty-fourth meeting in 2009).

The WHO Expert Committee on Specifications for Pharmaceutical Preparations discussed the need for a revision of both sets of guidelines at its forty-third meeting in 2008 and recommended that if the *Guidelines for good practices for national pharmaceutical control laboratories* were revised, the *Guidelines for preparing a laboratory information file* should be revised accordingly.

On the basis of the above and following the usual consultation process, the following text will replace the previously published guidelines.

1. General information on the laboratory	1191
2. Quality management system	1192
3. Control of documentation and records	1192
4. Personnel	1192
5. Premises	1193
6. Equipment	1194
7. Materials	1194
8. Subcontracting of testing	1194
9. Handling of samples	1195
10. Validation of analytical procedures	1195
11. Investigation of out-of-specification results	1195
12. Stability testing (where applicable)	1195
13. Microbiological testing (where applicable)	1195

A laboratory information file (LIF) is a document prepared by the laboratory. It contains specific and factual information about the operations carried out at the named site and any closely integrated operations of the laboratory. If only some of the operations are carried out on the site, the LIF needs to describe only those operations, e.g. sampling, chemical analysis or stability testing.

An LIF should be written in English, succinct and, if possible, should not exceed 30 A4 pages, excluding appendices.

The laboratory should give a short description of its activities under each of the following headings. Policy or essential steps for each activity should be described and reference to a standard operating procedure (SOP) or other supporting documents should be given, where applicable. Where appropriate, supportive documentation should be appended.

1. General information on the laboratory

- 1.1 Brief information on the laboratory (including name, physical (location) and mailing address, contact details and brief history). If the laboratory is part of an organization or company, provide details of its position within the organization or company, including reporting lines (e.g. organizational chart).
- 1.2 Summary of all laboratory activities, including objectives of the laboratory, categories of customers, types of sample tested. In addition, state the relation (if any) to a manufacturing site.
- 1.3 Areas of expertise proposed for prequalification (list methods and tests, for examples see the List of Prequalified Quality Control Laboratories).¹

Type of analysis	Finished products	Active pharmaceutical ingredients
Physical/chemical analysis		
Identification		
Assay, impurities and related substances		
Microbiological tests		
Bacterial endotoxin testing (BET)		
Stability testing		

¹ http://www.who.int/prequal/lists/PQ_QCLabsList.pdf.

- 1.4 Brief description of a policy for participation in proficiency testing schemes and collaborative trials and for the evaluation of the performance. Attach the list of tests in which the laboratory has participated in the last three years, including the organizer and results.

2. Quality management system

- 2.1 Short description of the quality management system implemented in the laboratory, including reference to the standard used (such as *WHO good practices for pharmaceutical quality control laboratories*, ISO 17025, good manufacturing practices) and existence of a quality manual.
- 2.2 Information on inspections carried out by national or regional authorities and external audits performed in the laboratory in the last three years, including reference to valid accreditation, certificate, authorization or licence.
- 2.3 Brief description of the procedures for internal audits, implementation of corrective and preventive actions and complaints.

3. Control of documentation and records

- 3.1 Brief description of the procedures for the control of and changes to documents that form a part of the quality documentation. Attach a list of valid SOPs.
- 3.2 Brief description of the procedures for the preparation, revision and distribution of necessary documentation for specifications, standard test procedures, analyst workbooks or worksheets.
- 3.3 Brief description of any other documentation related to product testing, including reports, records, arrangements for the handling of results (including laboratory information management systems (LIMS), where used).
- 3.4 Brief description of the procedures for release of certificates and analytical reports.

4. Personnel

- 4.1 Number of employees engaged in the following activities:

Activity	Number
Supervisors	
Chemical sector	
analysts	
technicians	
Microbiological sector	
microbiologists	
technicians	
Quality assurance staff	
Staff trained for sampling	
Other	
Total number of employees in the laboratory:	

- 4.2 Organization chart showing the arrangements, responsibilities and reporting lines in the laboratory.
- 4.3 Qualifications, experience and responsibilities of key personnel.
- 4.4 Outline of arrangements for initial and ongoing training and its recording.

5. Premises

- 5.1 Simple plan or description of the layout of the laboratory areas with an indication of scale (architectural or engineering drawings not required, but photographs may be submitted if available).
- 5.2 Nature of construction and finishing.
- 5.3 Brief description of ventilation systems including those for microbiological testing areas, storage areas, etc. (Include reference to air circulation and control of temperature and relative humidity.)
- 5.4 Brief description of special areas for the handling and storage of hazardous materials such as highly toxic (including genotoxic), poisonous and flammable materials.
- 5.5 Description of planned programmes for preventive maintenance of the premises and the system for recording maintenance activities.

- 5.6 Brief description of the procedures for cleaning of areas and equipment.
- 5.7 Short description of the storage areas (size, location) including arrangements for the storage of materials and retention samples.

6. Equipment

- 6.1 Brief description of the main equipment used in the laboratory. Attach a list of equipment in use, in tabular form, indicating the equipment and its brand model and date of installation.
- 6.2 Brief description of the planned programme for the preventive maintenance of equipment and the system for recording the maintenance activities.
- 6.3 Brief description of arrangements and status for qualification of equipment (installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ)) as well as calibration of measuring equipment, including the recording system.
- 6.4 Brief description of computer system and its validation and data integrity management, including access to data and frequency of back-up.

7. Materials

- 7.1 Brief description of general policy for purchasing and handling of materials (including chemicals and reagents and availability of safety data sheets) and for handling of waste. Brief description of the procedure for selection and evaluation of suppliers.
- 7.2 Brief description of the water system in the laboratory, its qualification and arrangements for the sampling and testing of the water.
- 7.3 Brief description of the system for purchasing, preparation, handling and storage of reference substances and reference materials.

8. Subcontracting of testing

- 8.1 List of activities contracted out to other laboratories, including names and addresses of subcontractors of subcontractors. Description of the way in which the compliance with standards for activities contracted out is assessed.

9. Handling of samples

- 9.1 Brief description of general policy for sampling. If the laboratory is responsible for sampling describe briefly the procedures used and standards applied.
- 9.2 Brief description of the procedures for handling of samples from their receipt to storage after completion of testing. Where possible, flow charts describing important steps and work allocation in the laboratory should be supplied.

10. Validation of analytical procedures

- 10.1 Brief description of general policy for validation of analytical methods, including verification of pharmacopoeial methods or analytical procedures validated by manufacturers

11. Investigation of out-of-specification results

- 11.1 Brief description of the procedure for recording and investigation of out-of-specification results.

12. Stability testing (where applicable)

- 12.1 Brief description of the stability testing procedure.
- 12.2 Brief description of the conditions under which samples are kept, the arrangements for monitoring and the equipment used.

13. Microbiological testing (where applicable)

- 13.1 Brief description of the activities for microbiological testing.
- 13.2 Brief description of preparation and control of media and types of media used.
- 13.3 Brief description of the procedure in place for positive and negative controls.
- 13.4 Brief description of validation policy.
- 13.5 Brief description of arrangements for waste disposal.

5.5 General guidelines for the establishment, maintenance and distribution of chemical reference substances

Annex 3, WHO Technical Report Series 943,
2007

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Introduction

In 1975 the WHO Expert Committee on Specifications for Pharmaceutical Preparations recommended the “General guidelines for the establishment, maintenance and distribution of chemical reference substances” (1). At that time these general guidelines were aimed at fostering greater collaboration and harmonization among various national and regional authorities responsible for collections of chemical reference substances. This aim is still relevant. The guidelines were initially drawn up specifically for use by the WHO Collaborating Centre for Chemical Reference Substances in Sweden, which supplies International Chemical Reference Substances (ICRS). These substances are primarily intended for use with pharmacopoeial monographs included in *The International Pharmacopoeia* (2).

It became evident that to ensure ready availability and cost-effectiveness, and in order to meet particular national or regional pharmacopoeial requirements, it was necessary to establish chemical reference substances external to the WHO Collaborating Centre for Chemical Reference Substances. Since the meticulous work of the WHO Collaborating Centre establishing the international collection would have to be duplicated in local or regional laboratories, guidelines were necessary to ensure the integrity of national or regional collections. The 1975 guidelines were reviewed and modified in 1982 (3) and subsequently revised in 1999 (4).

In 2004, the WHO Expert Committee on Specifications for Pharmaceutical Preparations recommended the development of more detailed guidelines on the establishment of secondary chemical reference substances. This additional guidance forms part B of the present revision and is intended to apply to secondary reference substances supplied as “official”, e.g. regional/national standards, and not to the working standards of manufacturers or other laboratories. However, in principle, secondary reference standards prepared by manufacturers can be prepared as “working standards” using the same procedures.

The purpose of establishing chemical reference substances is to achieve accuracy and reproducibility of the analytical results required by pharmacopoeial testing and pharmaceutical control in general. These substances are normally prepared and issued by the regional or national pharmacopoeia commission or the regional or national quality control laboratory on behalf of the drug regulatory authority. In the context of these guidelines, the general use of a chemical reference substance should be considered an integral part of a compliance-oriented monograph or test procedure used to demonstrate the identity, purity and content of pharmaceutical substances and preparations.

The purpose of establishing secondary reference substances is for use in routine analysis to determine the identity, purity and, in particular, the content of pharmaceutical substances in pharmaceutical preparations. The extent of characterization and testing of a secondary reference substance is less than that for a primary reference substance.

It is essential that a secondary reference substance is traceable to a primary reference substance, such as a pharmacopoeial or other officially recognized reference substance. In the cases of doubtful results or dispute when using secondary chemical reference substances, the test should be repeated using the primary standard.

The establishment of a chemical reference substance is based on the evaluation of the results of analytical testing. The report should subsequently be approved and adopted by a certifying body, normally the relevant pharmacopoeial committee or drug regulatory authority. The establishment of the reference substance can be on an international, national or regional basis. Each substance is generally established for a specific analytical purpose, defined by the issuing body. Its use for any other purpose becomes the responsibility of the user and a suitable caution is included in the accompanying information sheet. The present guidelines are concerned with both primary and secondary chemical reference substances as defined below.

The preparation of a chemical reference substance should comply with the requirements for quality assurance systems, including applicable principles of good manufacturing practices (GMP) and good control laboratory practices (5–10). Adequate training programmes are also required. Both the WHO Collaborating Centre and other laboratories concerned with the evaluation and establishment of chemical reference substances give assistance in training, subject to the availability of resources.

Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

chemical reference substance

The term *chemical reference substance*, as used in this text, refers to an authenticated, uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use.

primary chemical reference substance

A designated primary chemical reference substance is one that is widely acknowledged to have the appropriate qualities within a specified context, and whose assigned content when used as an assay standard is accepted without requiring comparison with another chemical substance.

secondary chemical reference substance

A secondary chemical reference substance is a substance whose characteristics are assigned and/or calibrated by comparison with a primary chemical reference substance. The extent of characterization and testing of a secondary chemical reference substance

may be less than for a primary chemical reference substance. Although this definition may apply *inter alia* to some substances termed “working standards”, part B of these guidelines is intended to apply to secondary reference substances supplied as “official”, e.g. regional/national standards, and not to manufacturers’ or other laboratories’ working standards.

International Chemical Reference Substance

International Chemical Reference Substances (ICRS) are primary chemical reference substances established on the advice of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. They are supplied primarily for use in physical and chemical tests and assays described in the specifications for quality control of drugs published in *The International Pharmacopoeia* or proposed in draft monographs. The ICRS may be used to calibrate secondary standards.

pharmacopoeial reference standards

The specificity of pharmacopoeial reference substances has been addressed in the introduction of *ISO Guide: General requirements for the competence of reference material producers*. “Pharmacopoeial standards and substances are established and distributed by pharmacopoeial authorities following the general principles of this Guide. It should be noted, however, that a different approach is used by the pharmacopoeial authorities to give the user the information provided by certificate of analysis and expiration dates” (9).

Part A.

Primary chemical reference substances

A.1 Assessment of need for the establishment of chemical reference substances

The production, validation, maintenance and distribution of chemical reference substances is a costly and time-consuming undertaking. It is, therefore, crucial to determine for certain whether a need for a given substance exists. Requests for new chemical reference substances usually arise when a particular approach to developing a specification for a new substance or product has been adopted. Methods may have been proposed in a specification that require the establishment of a chemical reference substance for use as a comparative standard. Therefore, the first matter that should be assessed is whether an alternative, equally satisfactory, procedure could be adopted that does not require a comparative standard.

Analytical procedures currently used in specifications for pharmaceutical substances and products that may require a chemical reference substance are:

- infrared (IR) spectrophotometry, whether for identification or quantitative purposes;

- quantitative methods based on ultraviolet (UV) absorption spectrophotometry;
- quantitative methods based on the development of a colour and the measurement of its intensity, whether by instrumental or visual comparison;
- methods based on chromatographic separation for identification or quantitative purposes;
- quantitative methods (including automated methods) based on other separation techniques that depend on partition of the substance to be determined between solvent phases, where the precise efficiency of the extraction procedure might depend upon ambient conditions that occasionally vary and from laboratory to laboratory;
- quantitative methods, often titrimetric but sometimes gravimetric, that are based on non-stoichiometric relationships;
- assay methods based on measurement of optical rotation; and
- methods that might require a chemical reference substance consisting of a fixed ratio of known components (for example, *cis/trans* isomers, spiked samples).

A.2 Obtaining source material

Source material of satisfactory quality can be selected from a batch (lot) of the substance originating from the normal production process, if the purity is acceptable. Further purification techniques may be needed to render the material acceptable for use as a chemical reference substance.

The purity requirements for a chemical reference substance depend upon its intended use. A chemical reference substance proposed for an identification test does not require meticulous purification, since the presence of a small percentage of impurities in the substance often has no noticeable effect on the test.

On the other hand, chemical reference substances that are to be used in assays should possess a high degree of purity. As a guiding principle, a purity of 99.5% or higher is desirable, calculated on the basis of the material in its anhydrous form or free of volatile substances. However, where the selectivity of the analytical procedure for which the chemical reference substance is required is low, such a degree of purity may not be necessary. In making a decision about the suitability of a chemical reference substance, the most important consideration is the influence of the impurity on the attribute measured in the assay when used in a non-specific assay procedure. Impurities with physicochemical characteristics similar to those of the main component will not diminish the usefulness of a chemical reference substance, whereas even traces of impurities with significantly different properties may render a substance unsuitable for use as a chemical reference substance.

When source material to be used as a chemical reference substance is obtained from a supplier, the following should be supplied with the material:

- certificate of analysis with complete information on test methods employed, values found and number of replicates used, where applicable, and relevant spectra and/or chromatograms;
- results of any accelerated stability studies;
- information on optimal storage conditions required to ensure stability (temperature and humidity considerations);
- results of any hygroscopicity study and/or statement of the hygroscopicity of the source material;
- identification of impurities detected and/or specific information on the relative response factor as determined in compendial methods concerning the principal component, and/or the percentage mass of the impurity;
- updated material safety data sheet outlining any health hazards associated with the material.

For new drug substances, manufacturers should be aware that elaboration of pharmacopoeial monographs will be necessary, and a batch of the new substance should be set aside to be used if necessary as the chemical reference substance. It is desirable for bodies that issue chemical reference substances to share the same batch of material, even if the substance will be employed for different test methods. This will require exchange of information concerning the establishment process, supplier(s), availability and conditions of supply.

A.3 Evaluation of chemical reference substances

The suitability of a substance proposed for use as a chemical reference requires careful evaluation by the issuing body. It is necessary to consider all data obtained from testing the material by a wide variety of analytical methods. When taken as a whole, this will ensure that the substance is suitable for its intended use. The extent of the analyses required depends on the purpose(s) for which the chemical reference substance is to be employed, and may involve a number of independent laboratories.

A.3.1 Use in identification tests

For use in identification tests (IR spectrophotometry and/or chromatographic methods), a batch of good quality material selected from the normal production process is satisfactory if it is of acceptable purity. Additional purification by the supplier may be necessary. The most important check is the application of the test(s) for which the substance is intended. It is usual for at least one laboratory to apply all the chemical and physical tests

described in the relevant monograph; some tests, such as those for sterility or for bacterial endotoxins, may not be necessary for materials intended as reference standards.

A.3.2 Use in purity tests

The characterization of a chemical reference substance for use in the determination of a specific impurity is more extensive, especially when used in a limit test. If the technique employed is thin-layer chromatography (TLC), an acceptable minimum purity is recommended (normally at least 90%), but purer material (at least 95%) may be required for liquid chromatography (LC) or gas chromatography (GC). It is usually enough to involve only one laboratory when the reference substance is used in purity tests. If the proposed reference substance is being prepared or isolated for the first time, appropriate chemical and physicochemical tests, such as nuclear magnetic resonance (NMR), mass spectrometry (MS) and elemental analysis, must be applied to characterize it.

A.3.3 Use in assays

If the chemical reference substance is to be used in an assay (colorimetry, LC, GC or UV spectrophotometry), the extent of testing is much greater. Several (a minimum of three) laboratories should collaborate in testing the proposed substance, using a variety of established and validated techniques, including the method used in the pharmacopoeial specification. The relative reactivity or relative absorbance of the impurities present must be checked when a nonspecific assay method is employed, e.g. by colorimetry or UV spectrophotometry. When a selective assay method is employed, it is particularly important to determine the quantity of impurities. In such a case, it is best to examine the proposed reference substance by as many methods as practicable including, where possible, absolute methods. For substances that are acidic or basic a titration with alkali or acid is simple, but other reactions which are known to be stoichiometric may be used. Phase solubility analysis and differential scanning calorimetry may also be employed in certain cases.

The total of the determinations of water content, organic solvents, mineral impurities and organic components should amount to 100%. For most chemical reference substances intended for assays, the content may be expressed "as is". When establishing the chemical reference substance it is, therefore, essential to determine the content of water and residual solvents for a non-specific assay, and also to determine the content of impurities for a selective assay.

A.3.4 Use in the calibration of an instrument

Where the chemical reference substance is to be employed as calibration material, the extent of testing is similar to that for a chemical reference substance used in assays. Several laboratories should collaborate in testing the proposed substance using a variety of techniques to check that its purity is adequate. An appropriate number of collaborating laboratories should also participate, after the reference substance has been

deemed suitable, to establish a value for the essential property of the substance using an appropriate instrument.

A.4 Chemical and physical methods used in evaluating chemical reference substances

It is important to establish by individual testing that a substance proposed for use as a chemical reference is suitable for that purpose.

The methods used to establish the suitability of such a substance fall into two broad groups: those intended primarily to identify the substance and those used to establish its purity. With most methods, the percentage purity of a chemical reference substance cannot be expressed as an absolute value if the impurities have not been identified. The quoted purity is then an estimate based upon the data obtained by the various analytical methods.

A.4.1 Methods used to verify the identity of chemical reference substances

Where a proposed reference substance is a substance whose structure has been satisfactorily defined, its identity may be confirmed by matching the IR spectrum of the substance to that of an authentic specimen. Particular care should be taken when polymorphism exists (8). Other highly specific techniques, such as NMR spectroscopy, MS, or X-ray diffraction crystallography, may also be used for such comparisons. The identity of a substance that is intended to replace an established chemical reference substance of the same molecular constitution must be verified, to determine that the characteristic properties of the two specimens are identical. For this purpose it is often sufficient to compare their IR absorption spectra.

However, where no authentic specimen of the proposed substance is available for comparison, and definitive data about its properties are lacking, it may be necessary to verify its identity by applying several of the analytical techniques currently used to characterize new compounds. Such analytical methods may include elemental analyses, crystallographic studies, MS, NMR spectroscopy, functional group analyses, and IR or UV spectrophotometry, as well as other supplementary tests, as required, to establish that the proposed substance is fully characterized.

A.4.2 Methods used to determine the purity of chemical reference substances

The analytical methods to be employed in examining a substance should be considered in relation to its intended use. These analytical methods may be divided into three broad categories:

- those that require comparison with an external chemical reference substance (e.g. chromatographic or spectrophotometric methods);
- those that depend solely on an intrinsic dynamic property (e.g. phase solubility analysis and differential scanning calorimetry); and
- other methods.

A.4.2.1 Separation techniques

The methods used for the determination of purity should be established and validated with system suitability requirements as appropriate.

Chromatographic methods. Methods of analysis based on chromatographic separation are especially useful for detecting and determining impurities in chemical reference substances. High-performance liquid chromatography (HPLC) is the most widely used chromatographic method, but TLC and GC are also used. The individual components separated by chromatographic methods may sometimes be recovered for characterization.

The selectivity of HPLC and of GC usually exceeds that of TLC. Both of the first two methods also have the advantage of being readily applicable on a quantitative basis, but they require more complex equipment. HPLC, employing a spectrophotometric method of detection, is of particular value in the examination of chemical reference substances intended for use in UV spectrophotometric assays. The UV wavelength of detection employed for determining the impurity content of the chemical reference substance should be chosen so that the detection responses of the substance and its impurities are similar. When the response factors are significantly different at the optimal wavelength of detection, appropriate corrections must be made to estimate the content of impurities. LC with diode-array detection is very useful for recording the UV spectra of both the main peak and the impurities. LC with MS detection is used for identification of separated impurities as well as for the main component, and is particularly important for use with chemical reference substances for which no other reference standards or IR reference spectra are available.

In a GC method used for an assay, as with LC, the detection responses of the impurities are determined. Generally, monograph methods using GC are of particular value in detecting and determining volatile impurities, including solvent residues, in chemical reference substances.

TLC uses apparatus that is simple and inexpensive; the technique is easy to carry out and is readily applicable even in the microgram range. It can separate closely related compounds, such as geometric isomers and the members of a homologous series. All the constituents of a substance subjected to chromatography appear somewhere on the chromatogram. However, some constituents may remain on the starting line, some may move with the solvent front, some may migrate at the same rate as the main component and some may remain undetected. For this reason, the usefulness of the method may

be greatly enhanced by performing two-dimensional chromatography and by using a number of different solvent systems and a variety of detection methods. In some cases the method may be used quantitatively with acceptable accuracy by using a densitometer.

Capillary electrophoresis. Capillary electrophoresis (CE) is an increasingly common method. It may be considered as complementary to LC for detecting impurities.

A.4.2.2 Methods based on intrinsic thermodynamic properties

Methods in this group measure total impurity levels in absolute terms.

Differential scanning calorimetry. This technique is used to check for the presence of different polymorphic forms and to determine the total amount of solid impurities. Purity estimation is based on determination of the heat of fusion of the sample and of the change in its melting point caused by the presence of impurities. This analytical method can be performed rapidly and with high precision. However, it is not applicable if the substance decomposes on melting. This limits its value as a general procedure for estimating the purity of chemical reference substances. It is also inapplicable if solid solutions are formed.

Phase solubility analysis. The method has occasionally been used but its value is limited and the procedure is time consuming. It may be employed to detect contaminating substances, including isomeric species, and to estimate their concentration. Some factors that may make the method inapplicable are degradation of the substance during the course of analysis, formation of a solid solution and polymorphism in the main component.

A.4.2.3 Other methods

Spectrophotometric methods. UV spectrophotometry is occasionally used to determine purity. Since it depends upon the presence of a characteristic chromophore, it can detect impurities that contribute excessively to the absorbance value and may indicate the presence of impurities that have a negligible or distinctive absorbance.

However, the utility of the method is limited by the small number of absorption maxima in the UV range, the large numbers of compounds containing similar characteristic chromophores, and the need for an external chemical reference substance.

IR spectrophotometry may be used to identify and determine the proportions of geometric isomers. NMR spectroscopy, a powerful spectroscopic identification tool, is also occasionally useful in the determination of purity.

Titrimetric methods. Titrimetric methods provide a valuable means of confirming the identity and purity of a proposed chemical reference substance and are useful in confirming purity values obtained by other methods.

Optical rotation methods. Many chemical reference substances are optically active and the relative proportion of optical isomers can sometimes be determined by an optical rotation method, but generally such methods lack specificity and sensitivity.

However, the quantitative use of these techniques is well established and can yield results of high precision, depending on the solvent and the wavelength chosen for measurement, provided that pure substances of individual isomers are available. Chiral chromatography, NMR and CE are becoming increasingly important.

Determination of water and organic volatiles. It is essential that an accurate assessment of the moisture content and the content of volatile substances be made. These total values may often be obtained by drying under defined conditions that are appropriate to the proposed substance. Sometimes this may not be possible or may yield misleading results. In such cases, thermogravimetric analysis may be used to determine the content of water and organic volatiles. Alternatively, the water content may be determined by Karl Fischer titration and the content of volatile solvents by GC. Without an accurate assessment of these values at the time that other determinations are being made, judgements of the acceptability of the proposed chemical reference substance will be invalid.

A.5 Assignment of content

If a content is to be assigned to a chemical reference substance, it should be borne in mind that the value is based on the results of a collaborative interlaboratory programme using different analytical methods. This experimentally obtained value represents the best estimate of the true value. In general, the value must be further corrected for the fraction of impurity. Sometimes the chemical reference substances must be dried before use, in which case the content is expressed on the basis of the dried material.

A.6 Handling and distribution of chemical reference substances

The handling, distribution and use of established chemical reference substances must ensure that their integrity is safeguarded and maintained throughout their period of use.

A.6.1 Packaging operations

Appropriate GMP requirements (6) should be observed. The various stages in packaging chemical reference substances should be clearly defined and controlled, to avoid contamination of the sample, mislabelling of containers, or any other event which might result in mishandling or mismanagement.

Containers for chemical reference substances should protect their contents from moisture, light and oxygen and must be tested for permeability to moisture. Additional measures may be necessary to ensure long-term integrity and stability. Most chemical reference substances, however, are conveniently supplied in moisture-proof containers which should be uniform in type and size to facilitate distribution. The lack of permeability to

moisture and the compatibility of the material of which the closure is made with the chemical reference substance are important factors in determining the suitability of container closure systems. The best containers for chemical reference substances from the point of view of stability are sealed glass ampoules, but these have certain disadvantages. There is a risk of contaminating the substance with glass particles when the ampoules are opened.

It is preferable to restrict the quantity of reference substance held in each container to that required to perform the test(s). The use of multidose containers is not excluded, but is not recommended.

Before undertaking any packaging operations, the health hazards of the item to be packaged should be assessed using suitable information sources, e.g. the material safety data sheet. Appropriate precautions should be taken to protect the person(s) handling the chemical reference substance.

The packaging of a batch of a chemical reference substance into containers is a small-scale operation for which suitable equipment is not always available to the manufacturer of the material. Therefore, the packaging of chemical reference substances is usually undertaken by the responsible issuing body. Screw-type feeders have been constructed, but generally the packaging of chemical reference substances is carried out manually. Substances which are expensive or available only in very small quantities may have to be divided between containers in solution and then lyophilized, or evaporated to dryness.

Some chemical reference substances must be packaged under an inert gas or in conditions of controlled humidity. Therefore, the use of a glove-box or an air-tight cabinet is necessary. Single-use vials can be used for hygroscopic materials.

A.6.2 Storage

Information about suitable storage conditions can often be obtained from the manufacturer of the source material and should be requested routinely when a new chemical reference substance is established. Theoretically, the stability of the substances should be enhanced by keeping them at low temperatures but, for substances that contain water, storage below 0 °C may impair the stability. It should also be remembered that the relative humidity in normal refrigerators or cold rooms may be high and, unless ampoules or other tightly closed containers are used, the improvement in stability may be more than offset by degradation due to the absorption of moisture. Storage at about 5 °C, with precautions to prevent such absorption, has proved satisfactory for most chemical reference substances. Vials should, however, not be opened until they have attained room temperature to prevent ingress of moisture by condensation.

A.6.3 Stability

A chemical reference substance is an integral part of the drug specification. Thus, if the reference substance deteriorates, this will change the specification of the drug. It is, therefore, of the utmost importance that the stability of chemical reference substances

is monitored by regular re-examination and that they should be replaced as soon as a significant change in a property is noted.

The definition of a “significant change” differs according to the intended use of the chemical reference substance. Several per cent of degradation products found in a substance may not impair the usefulness of the material in identification tests. For chemical reference substances that are used in chromatographic assays, however, even small amounts of impurities may be unacceptable. When establishing a chemical reference substance, consideration must be given to its intended use and to the performance characteristics of the analytical methods in which it will be used. The tolerable degree of degradation will differ from case to case but should be predefined.

Laboratories in charge of collections of chemical reference substances should have a system for regular re-examination of the materials in stock. The frequency of re-testing may be modified according to need. It must be borne in mind that the stability of a specially prepared chemical reference substance may not always be the same as that of commercial samples of the same material.

The selection of suitable analytical methods for monitoring the stability of chemical reference substances depends on the nature and intended use of the substance. A substance used solely for identification purposes will normally only require demonstration that it is still suitable for this use, e.g. that the IR spectrum is identical to that obtained during establishment. If substances are employed for other purposes, the testing must be more extensive, but should use methods which are rapid and sensitive so as not to consume too much of the existing stock. In many cases it is important to check that there has been no significant uptake of moisture, which could result in degradation by hydrolysis and/or a decrease in the assigned content of the substance. Chromatography is employed extensively, as are absolute methods such as differential scanning calorimetry where applicable. Changes in the impurity profile or purity determination usually mean that the batch must be replaced. Changes which compromise the integrity of the batch indicate that it should immediately be withdrawn from use. Sometimes a batch of a chemical reference substance will discolour or otherwise change in appearance. Steps should be taken to replace this substance whether or not the results of subsequent analyses indicate significant degradation. Such changes in physical appearance reduce the confidence of the user in the suitability of the chemical reference substance. Appropriate testing of active bulk substance should be carried out before further dispensing into vials or ampoules.

A.6.4 Information to be supplied with chemical reference substances

The labels on chemical reference substances should give the following information:

- the appropriate name of the substance: the international nonproprietary name (INN) should be used wherever possible;
- the name of the issuing body;

- the approximate quantity of material in the container; and
- the batch or control number.

Where associated documents are provided they should incorporate relevant items from the list above. The following information should be given, as necessary, on the labels and/or in associated documents:

- the name and address of the issuing body;
- the recommended storage conditions (if special conditions apply);
- the intended use of the chemical reference substance;
- directions for use (e.g. storage and handling);
- information about the assigned analytical value of the chemical reference substance (needed for calculation of the results of tests in which the substance will be used);
- a disclaimer of responsibility in cases where chemical reference substances are misused, or stored under inappropriate conditions, or used for purposes other than those intended by the issuing body; and
- health hazard information or warnings in conformity with national and regional regulations or international agreements.

If analytical data are to be supplied with the chemical reference substances, it is recommended that the data provided be limited to what is necessary for the proper use of the substances in the tests and assays.

A.6.5 Distribution and supply

Distribution of chemical reference substances within the same country usually does not present problems. However, when samples are to be sent to other countries, both the sender and the receiver of the goods may encounter difficulties because of the vagaries of postal and customs regulations, e.g. the application of special procedural requirements applicable to substances under international control. Distributors of chemical reference substances waste considerable resources in seeking information on different international import regulations, and in completing the required forms. A way of reducing such difficulties and barriers to effective distribution of chemical reference substances should be sought. There should be a minimum of delay in providing the chemical reference substances to the users, and the most speedy means of transport should be chosen.

A.6.6 Period of use

Chemical reference substances do not carry an “expiry date” in the conventional sense. To avoid the unnecessary discarding of satisfactory substances, a mechanism for general control of the batch of a chemical reference substance may be used by the issuing

body. If the issuing body applies stability considerations and a monitoring procedure to its collection based on its experience, this should be a guarantee to the user of the acceptability of the chemical reference substance for its intended use.

Whenever a batch of primary reference standards needs to be replaced, the issuing body should, wherever practical, allow for a transition period.

If, exceptionally, it is considered necessary to specify an expiry or re-test date, this should be stated on the label and/or in a document accompanying the chemical reference substances. Adequate shipping records should be kept to enable contact to be made with the purchaser of a batch for recall or other notification.

The storage and maintenance of unopened containers of the chemical reference substance in accordance with the information provided are integral to its suitability for use. To avoid potential doubts concerning the integrity of opened containers, it is suggested that potential users obtain only the quantities of substances necessary to meet their short-term needs and to obtain fresh stocks (held under controlled and known conditions) when required. Long-term storage of substances in opened containers should be avoided. Similarly, efforts should be made to avoid possible degradation, contamination and/or introduction of moisture during the repeated use of portions of a substance from the same container.

Part B.

Secondary chemical reference substances

This new Part B is intended to apply to secondary reference substances supplied as “official”, e.g. regional or national standards. In principle, secondary reference standards prepared by manufacturers can be prepared as “working standards” using the same procedures.

B.1 Assessment of need

The establishment of a secondary chemical reference substance, calibrated against a primary reference standard substance, may be desirable for various practical reasons, e.g. the primary standard may not be available in adequate quantities to supply all local needs. Moreover, the availability of such secondary chemical reference substances (for example, on a regional basis) would reduce the cost and the delay in receiving the reference material.

The body that establishes a secondary chemical reference substance for national or regional use should be clearly defined by the appropriate regional or national drug regulatory authority. The traceability between the secondary and the primary chemical reference substance must be documented.

B.2 Obtaining source material

B.2.1 Selection of candidate substance

When it is intended to establish a secondary reference substance for use as an assay standard for the determination of the content of the drug substance itself or in a drug formulation, a source(s) of pharmaceutical grade substance(s) is (are) identified. Availability of the required quantity is assured. The guidelines given in Section 2 of Part A also apply in this case. If a substance is intended to be used as an impurity standard, the candidate material may be obtained from commercial suppliers, provided that the percentage purity is more than 95% (or 90% if for use in TLC).

B.2.2 Documentation to be supplied with the candidate reference substance

The supplier of the candidate reference substance is requested to supply the same documentation as required for a candidate primary reference substance (see Section 2, Part A).

B.2.3 Initial testing for compliance with the requirements of the monograph

The coordinating laboratory is responsible for verifying that the candidate reference substance complies with the requirements of the monograph, where applicable. In such a case compliance is a prerequisite to proceeding to the interlaboratory study to assign the content of the secondary standard.

B.3 Packaging

See Section 6.1 in Part A of these guidelines.

B.4 Interlaboratory testing to establish the assigned content

Having demonstrated the suitability of the substance, the content value is assigned on the basis of the results generated by an interlaboratory trial. At least three laboratories participate in testing the proposed substance (10).

B.4.1 Competence of the participating laboratories

Participating laboratories will have demonstrated their adherence to the concepts of an appropriate quality management system (9–12).

B.4.2 Dispatch of the candidate materials

The proposed secondary reference substance is packaged in appropriate unit quantities. The quantity of each unit is dependent on the intended use. The proposed substance and the primary reference substance are dispatched to the participating laboratories in sufficient amounts for replicate analysis as required by the test protocol. The participating laboratories are instructed to record any abnormalities observed with the proposed substance. The packaging facilities are adequate and environmental conditions are controlled to ensure the integrity of the material throughout the packaging process.

The following documents should be supplied with the material:

- test protocol;
- test result report form;
- health and safety information; and
- information on the primary chemical reference substance.

B.4.3 Test protocol

While the testing of primary chemical reference substances employs different analytical methods in a collaborative study, an alternative approach is normally applied to the testing of a secondary chemical reference substance. Since most secondary reference substances are established to determine the content of the drug substance itself (for which a pharmacopoeial monograph exists) and/or the amount of the drug substance contained in a pharmaceutical preparation, it is essential to use the method specified in the relevant pharmacopoeia to obtain the assigned value.

The coordinating laboratory prepares the testing protocol, including predefined acceptance criteria of the results. The protocol clearly describes each step of the procedure and includes data reporting sheets. The experimental design of the interlaboratory study is such that the results are statistically evaluated to assign a content with an acceptable confidence interval in relation to the permitted limits of content as set in the definition. Both the number of independent replicate determinations to be performed and acceptance criteria to be applied are predefined.

B.4.4 Evaluation of test results

Test results submitted by the participating laboratories are evaluated in accordance with the criteria set out in the protocol. The data submitted by each laboratory are tested statistically for “outliers” and for conformity with the system suitability criteria. Apparent “outliers” are investigated by the laboratory concerned, remedial action taken, and the analysis repeated. If a valid reason is discovered for the “outliers” then these are excluded from the statistical evaluation.

The mean and confidence interval are then calculated. The reference value is assigned using the mean of the laboratory means.

B.4.5 Traceability

The term for “traceability”, for the purposes of this document, is defined as the property of a result of measurement which can be related to the appropriate standards, generally international or national standards, through an unbroken chain of comparison. In other words, when the result of a measurement is described as traceable, it is essential to specify to what (value of) “appropriate standards” traceability has been established.

The assigned value of a secondary chemical reference substance is traceable to the relevant primary reference substance. In the context of WHO quality specifications the relevant primary chemical reference substance is usually the ICRS established for use with *The International Pharmacopoeia*. In other contexts the relevant primary chemical reference substance will be the reference substance established for use with another internationally recognized pharmacopoeia (e.g. the European Pharmacopoeia chemical reference substances (Ph.Eur CRS), British Pharmacopoeia chemical reference substances (BPCRS), or the United States Pharmacopeia reference substances (USPRS)).

B.5 Adoption of the secondary reference substance

The report of the collaborative trial to establish the secondary reference standard is submitted to the appropriate national or regional body to approve the secondary standard for the uses described.

B.6 Retesting programme

See also Section 6.3 in Part A of these guidelines.

A system must be in place to ensure the continued fitness for use of the reference substances. Normally, a re-test programme is applied.

Reference substances are regularly tested for stability during their storage. A testing programme is applied which is designed to detect any sign of decomposition at an early stage using appropriate analytical techniques. The methods employed are suitable for small quantities, are both rapid and sensitive, and will have been performed during the establishment phase.

The frequency and extent of re-testing reference substances depends on a number of factors including stability, container and closure system, storage conditions, hygroscopicity, physical form and intended use. The frequency of testing and the testing methods to be employed for each reference substance must be documented.

Reference substances should preferably be subdivided and presented as single-use units. However, if the reference substance is kept in a multiuse container then re-testing will need to be more frequent because there is a greater risk of the uptake of moisture and/or decomposition of the reference substance. The testing methods should include the determination of water content and decomposition products. The maximum

permitted variation from the assigned value should be predefined and if exceeded the batch should be re-established or replaced.

If the batch of primary reference substance used to calibrate the secondary reference substance is replaced, the secondary reference substance must be recalibrated against the new batch of the primary reference substance.

B.7 Information to be supplied with secondary chemical reference substances

For details of the information to be supplied see Section 6.4 of Part A of these guidelines: “Information to be supplied with chemical reference substances”.

B.8 Period of use

The expiry date is not indicated for secondary reference substances because the substances comply, where applicable, with the requirement of the pharmacopoeial monograph and are monitored regularly according to the re-testing programme. The issuing body should have effective means of communication to inform users of the validity of reference substances. It is recommended that only an amount sufficient for immediate use be purchased, and that the substances are used as soon as possible. Once the container has been opened efforts should be made to avoid possible degradation, contamination and/or introduction of moisture and/or exposure to air.

B.9 Distribution and supply

The distribution of secondary reference substances is carried out in such a manner as to maintain the integrity of the substance and avoid unnecessary delay in delivery to the users. The following factors are taken into account:

- conformity with safety and transport requirements;
- export and import procedure when the substance is to be delivered outside the country of the issuing body;
- customs regulations, e.g. special requirements applicable to substances under international control; and
- means of transportation.

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6. Inspections

6.1 Quality management system requirements for national inspectorates

Annex 5, WHO Technical Report Series, 1025, 2020 (revised)

Background

During the Joint Meeting on Regulatory Guidance for Multisource Products (Copenhagen, July 2016), several World Health Organization (WHO) guidance documents were identified for update. In October 2016, the Fiftieth WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) confirmed the need to update the selected guidelines.

Following up on the recommendation from the Fiftieth ECSPP, the WHO Secretariat conducted a detailed analysis of the cluster of guidelines proposed for revision. The outcome of this analysis was discussed during the informal consultation on Good Practices for Health Products Manufacture and Inspection (Geneva, July 2018). In particular, considering that the *WHO Quality systems requirements for national good manufacturing practice inspectorates* (1) defines the basic requirements applicable to quality systems for the operation of inspection services within national regulatory authorities (NRAs) concerned with good manufacturing practices (GMP) inspections, the WHO Secretariat proposed a strategy for revision that includes aligning the guidance with the principles of ISO 9001:2015 (2) and with relevant Pharmaceutical Inspection Convention/Co-operation Scheme (PIC/S) guidance (3), as well as broadening its scope to include all good practices (GXP)-related inspections conducted by an NRA.

The Fifty-second ECSPP endorsed the proposal for revision and recommended the WHO Secretariat to revise the *WHO Quality systems requirements for national good manufacturing practice inspectorates* (1), aligning its content to international standards and the latest quality management systems (QMS) principles, and to expanding the scope.

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1. Introduction

- 1.1 This document describes the quality management system (QMS) requirements for the operation of inspection services within national regulatory authorities (NRA) or other state structures (for the purpose of this guidance, the term “NRA” will be used in the text to represent both NRAs and other state structures). It is intended that each inspection service uses these requirements as the basis for developing and implementing its own QMS. Where the inspectorate operates under the umbrella of the NRA QMS, consideration should be given to the *WHO guideline on the implementation of quality management systems for national regulatory authorities* (4).
- 1.2 The adoption of a common standard for QMS requirements is an essential element in achieving consistency in inspection practices and facilitating structured communication with other units of the NRA, as well as enabling mutual confidence and permitting recognition between pharmaceutical inspectorates.

2. Scope

- 2.1 This document outlines the QMS requirements for pharmaceutical inspectorates that are competent for the oversight of GXP operations.

3. Glossary

The definitions given below apply to the terms used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts.

corrective actions. Steps taken to eliminate the cause of existing nonconformities in order to prevent recurrence. The corrective action process tries to make sure that existing nonconformities and potentially undesirable situations do not happen again.

good practices (GXP). The group of good practice guides governing the preclinical, clinical, manufacturing, testing, storage, distribution and post-market activities for regulated pharmaceuticals, biologicals and medical devices, such as good laboratory practices (GLP), good clinical practices (GCP), good manufacturing practices (GMP), good pharmacovigilance practices (GPP) and good distribution practices (GDP).

internal audit. An examination and assessment of all or part of a quality system, with the specific purpose of improving it. An internal audit should be conducted by an independent (of the function to be audited) and qualified team of experts designated by the management for this purpose.

quality indicators. Selected data intended to be monitored and used in assessing trends in performance.

quality management system. An appropriate infrastructure, encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

quality manual. A document that includes the quality policy and objectives and describes the various elements of the QMS.

quality policy. A brief statement that describes the organization's purpose, overall intentions and strategic direction; provides a framework for quality objectives; and includes a commitment to meet applicable requirements.

rapid alert. An urgent notification submitted by an NRA participating in the rapid alert system concerning measures taken against a product placed on the market that poses a risk to consumers' health and/or safety.

risk management. The systematic application of quality management policies, procedures and practices to the tasks of assessing, controlling, communicating and reviewing risk.

standard operating procedure (SOP). An authorized written procedure giving detailed instructions for performing a task or following a process in accordance with legislation, official guidance or internal standards.

4. Quality management system

- 4.1 The concept of a QMS is wide-ranging and covers all matters that are necessary to implement the inspectorate's quality policy and to meet predefined objectives.
- 4.2 The QMS should define the inspectorate's scope and context within the regulatory mandate, as well as covering all functions, processes and activities.
- 4.3 The primary aims of an inspectorate's QMS are:
 1. to ensure its ability to consistently provide services that meet the organization's objectives, legal requirements and interested parties' expectations; and
 2. to facilitate continual improvement and provide a sound basis for sustainable development to comply with statutory and regulatory requirements.

- 4.4 The QMS should at least describe and manage organizational structure, responsibilities, procedures, systems, processes and resources required, to provide value and achieve results for the inspectorate and relevant interested parties.
- 4.5 Typically, the legal basis for the establishment of the inspectorate, its mandate, the quality policy and the principles of the QMS should be documented in a quality manual or equivalent document.
- 4.6 The QMS should enable senior (“top”) management to best use available resources and systems in order to achieve the inspectorate’s targets and quality objectives. Senior management’s commitment and active participation is essential to ensure implementation of the QMS and to support staff within the inspectorate.

5. Context of the inspectorate

- 5.1 The legal basis for the establishment of the inspectorate and its mandate, as well as statutory and regulatory responsibilities and functions, should be clearly defined.
- 5.2 The inspectorate should determine its scope and strategic direction, in order to achieve the intended objectives.
- 5.3 The structure and operation of the inspectorate should be such that impartiality and independence are safeguarded. Rules for deontology, confidentiality, ethics and conflicts of interest should be clearly defined and obeyed. Where relevant, the inspectorate should implement a policy that distinguishes between the process of inspection and that of providing an advisory service. This service should be of benefit to all of industry and not solely to individual organizations.
- 5.4 The relationship of the inspectorate with other departments within the same NRA, and other agencies and organizations outside the inspectorate, as well as any other stakeholders, should be described and documented where relevant.

6. Management and leadership

- 6.1 Senior management should make a formal commitment to the implementation of a documented quality policy that is compatible with statutory requirements and relevant objectives.
- 6.2 Senior management should ensure that the inspectorate’s services and functions are aligned with regulatory requirements and the NRA’s objectives, as well as meeting interested parties’ expectations.
- 6.3 Senior management is accountable for the integration of QMS requirements into the inspectorate’s processes and functions; for communicating the importance of

QMS principles; and for the overall effectiveness of the QMS. In addition, senior management should promote the application of risk management principles and support the engagement and contribution of personnel in improving the QMS.

- 6.4 Senior management should ensure that the pharmaceutical inspectorate has sufficient and appropriate resources at all levels to enable it to meet its objectives. Responsibilities, authorities and the reporting structure for relevant roles should be clearly defined and documented in the QMS. The structure should be defined in organization charts.
- 6.5 An appropriately experienced and qualified person should be nominated as a QMS responsible person. This person should have direct access to senior management. If necessary, this task may be assigned to more than one person.
- 6.6 There shall be a system for periodic management review of the QMS effectiveness, including process improvements. Such reviews should be documented and records should be maintained for a defined period.

7. Management system planning

- 7.1 The inspectorate should establish appropriate objectives for the intended level of service and of its functions, which should be consistent with the quality policy and regulatory requirements. Principles of risk management and sustainable development should be considered for the establishment of these objectives.
- 7.2 These objectives should be communicated to personnel at all levels and be updated whenever necessary.
- 7.3 Appropriate resources should be available to meet these objectives. Roles and responsibilities should be defined and, where appropriate, timelines for completion should be established. Systems for monitoring and evaluating results should be established. All necessary information on quality objectives should be maintained.
- 7.4 A documented change management system should be established, to ensure that change requests are assessed, approved or rejected; that appropriate resources are allocated; and that roles and responsibilities are defined. Any change should be documented, communicated to the personnel and evaluated after implementation, to ensure the objectives are met. The change management system should ensure that continual improvement is undertaken in a timely and effective manner.

8. Resources

- 8.1 The inspectorate should have an organizational structure, required resources (financial, human, facilities and others) and documented procedures that enable it to meet its objectives; to perform inspection activities in accordance with official GXP guidelines and national legislation; and to carry out its functions and operations satisfactorily. Where necessary, measures and resources for the safety of personnel should be available.

Personnel

- 8.2 The inspectorate should employ the required personnel possessing the appropriate expertise to perform its functions, including inspections, and to determine whether the inspected entities comply with the principles of current GXP guidelines and with relevant legislation.
- 8.3 Personnel responsible for inspections should have appropriate qualifications, including education, training, experience and knowledge of the inspection process and subject, and should be periodically evaluated. They should have the ability to make professional judgements as to the conformity of the inspected party with the requirements of GXP and the relevant legislation, and be able to apply risk management principles in their decision-making process.
- 8.4 The inspectorate should ensure that induction and continuous training is provided to inspection personnel on administrative, regulatory and technical topics, to maintain the inspectors' competency aligned with current industry practice, technological advancements and regulatory changes. Training should be documented and its effectiveness assessed periodically.
- 8.5 The inspectorate should maintain documented and up-to-date information on the relevant qualifications, training and experience of each inspector.
- 8.6 Personnel should have clear, up-to-date and documented job descriptions specifying their duties and responsibilities.
- 8.7 When products are procured from a third party and/or services are subcontracted to an external body or expert, the inspectorate should ensure that the third party meets predefined documented criteria, qualifications and the relevant requirements of the quality management system. Senior management should ensure that these external bodies or experts are periodically evaluated. Third party responsibilities and liability should be clearly defined in the contract or agreement.
- 8.8 All personnel employed or contracted by the inspectorate should be bound by the requirements of the quality system, obey the inspectorate's code of conduct and

not be subject to any commercial, financial or other pressures that might affect their judgement and freedom to act. They should not be under the control of the pharmaceutical industry and must be assessed for potential conflict of interest. Personnel and third-party declarations of conflict of interest should be maintained, reviewed periodically and updated where necessary. It should be ensured that any decision-making process remains with the inspectorate and is not influenced by any third party.

Infrastructure

- 8.9 Personnel should be provided with the necessary infrastructure and appropriate work environment to enable them perform their functions and meet the quality objectives. Infrastructure includes, but is not limited to:
- buildings, workspace and associated facilities;
 - qualified equipment, including hardware and software;
 - transportation resources; and
 - information and communication technology.

9. Documentation

General

- 9.1 The inspectorate should establish and maintain a system for the control of all documentation, including electronic files, relating to the inspectorate's QMS and activities. This should include policies, procedures, guidelines, records and any documents of external origin, such as legislation, which may directly or indirectly influence the activities of the inspectorate; or documents received from pharmaceutical companies and relevant organizations, as appropriate.
- 9.2 The inspectorate should ensure that its functions and operations are described in SOPs that clearly define the required responsibilities, processes and actions. These may include, but not be limited to, training; inspections; reporting after inspections; handling of complaints; licensing (issue, suspension, withdrawal); certification; handling of quality, safety and efficacy issues; documentation control; change and deviation management; inspection planning; risk management; and the handling of appeals.
- 9.3 The system and activities relating to advising on, issue, withdrawal or suspension of licences, registration or certifications; and the application of other regulatory sanctions on facilities, organizations, products or operations, should be detailed in procedures and be in accordance with relevant guidelines and national legislation.

- 9.4 The inspectorate should establish procedures describing communication with other NRA units and external interested parties (e.g. industry, media) considering any statutory and regulatory requirements, where appropriate. Similarly, a procedure for exchanging regulatory information with other NRAs or national quality control laboratories should be available.
- 9.5 Activities relating to the sampling and testing of pharmaceutical products and raw materials should be described in a procedure that should also include the process for handling nonconforming products (e.g. substandard or falsified medical products).
- 9.6 The inspectorate should have procedures on handling quality, safety and efficacy issues that may lead to recall or withdrawal of products from the market. Where applicable, the inspectorate should establish and maintain a system for communicating rapid alerts. Records of recalls and withdrawals should be maintained in accordance with national legislation.
- 9.7 The inspectorate should have documented procedures for dealing with complaints arising from its activities or those of its personnel and any contracted person or organization. A record should be maintained of all complaints received and the actions taken by the inspectorate. These records should be retained for a specified period of time.
- 9.8 The inspectorate should have procedures for consideration of appeals against its decisions.
- 9.9 The documentation control system should ensure that:
 - documents are identified by title, author, reviewer, approver and unique identification. They should be dated and authorized by the appropriate persons prior to issue;
 - current versions of documents are held by nominated personnel;
 - a register of all relevant documents and document holders is maintained;
 - superseded documents are withdrawn from use but are retained for defined periods of time;
 - any changes to documents are made in a controlled manner and are properly authorized. There should be a means of identifying changes in individual documents;
 - records relating to the inspectorate's activities and functions are readily available and are retained for an adequate period, in line with legal requirements or internal standards;
 - records comply with the relevant obligations under national legislation;

- records are safely stored during their retention period and held under conditions that guarantee their security and confidentiality unless otherwise required by national legislation. The destruction of records after their retention period should follow a predefined procedure; and
- electronic documentation and record management systems provide at least the same level of assurance, compliance, accuracy and security as a manual system.

Inspection process and documents

- 9.10 An inspection should be categorized in accordance with GXP guidelines (e.g. GMP, GDP, GCP) and its scope (e.g. product, process) and type (e.g. triggered, routine, follow-up) should be appropriately defined and documented.
- 9.11 The inspectorate should plan inspections in advance and elaborate a written programme as part of the inspectorate's annual workplan. Risk management principles should be considered when establishing an inspection programme and prioritizing inspections, as well as when conducting an inspection. Where repeated inspections of a company or organization have to be carried out, the frequency should be determined based on risk management principles defined in a procedure.
- 9.12 Inspection-related documents and records, as defined in relevant inspection procedures (e.g. inspection plan, aide-mémoire, checklists, worksheets and company documents and records), should be maintained for a defined period.
- 9.13 When more than one inspector is involved in an inspection, a lead inspector should be appointed to coordinate inspection activities. The inspection report should be prepared by the lead inspector, with the assistance of all participating inspectors and/or experts, and should be agreed upon by all participating inspectors and/or experts.
- 9.14 The inspection report should follow a pre-approved format. Observations and/or data obtained in the course of inspection should be recorded in a timely manner, in order to prevent loss of relevant information.
- 9.15 The inspection report should be sent to the inspected company or organization within the inspectorate's established timelines. The lead inspector and all concerned inspectors and/or experts should participate in assessing the company's response, to determine the appropriateness of corrective and preventive actions as well as the GXP compliance status of the company or organization.
- 9.16 Completed inspections should be reviewed to ensure that all reporting and regulatory requirements are met.

10. Operational planning and performance evaluation

- 10.1 An annual workplan should be developed, documented and periodically reviewed by senior management, including all the inspectorate's activities, in accordance with a written procedure. Regulatory, statutory and scientific requirements should be taken into account during the planning of operations and services. Consideration should also be given to the availability of required resources and the ability to consistently provide services that meet legislative requirements and stakeholder expectations. Risk management principles should be used during planning, to determine, monitor and manage risks and to identify opportunities for process improvements. Any changes to the workplan should follow the inspectorate's change management system.
- 10.2 Appropriate quality indicators and methods should be established, in order to monitor and periodically evaluate the inspectorate's processes and level of improvement and service (including contracted-out services) and demonstrate that they were carried out as planned and met predefined quality objectives. These quality indicators, methods, analyses and results should be documented.
- 10.3 The results of the analyses should be used to evaluate the performance and effectiveness of the QMS, the adequacy of actions taken to address risks, and the need for further improvements.

Internal audits

- 10.4 The inspectorate should implement a system of periodic and documented internal audits of its operations, to assess compliance with the requirements of the QMS. Internal audits should be conducted at least once a year.
- 10.5 Internal audit processes, criteria, scope and documents should be defined. Auditors' qualifications and selection criteria should be documented. Internal audit records, including the findings, conclusions, recommendations and follow-up actions, should be retained for a defined period.
- 10.6 Corrective actions corresponding to audit findings should be identified, documented and implemented in a timely manner. The effectiveness of these actions should be evaluated and the risk plan should be updated to take note of the root causes of the nonconformances.

Management review

- 10.7 Senior management should review the inspectorate's QMS at planned intervals, to ensure its continuing suitability, adequacy, effectiveness and alignment with

the inspectorate's strategic direction and legislative requirements. Management reviews should be conducted at least once a year.

10.8 A management review should include, but not be limited to:

- the status of the actions from previous management reviews;
- any internal or external changes affecting the QMS;
- any deviations affecting the functionality of the QMS;
- the extent to which quality objectives have been met;
- process performance analyses;
- audit results and the effectiveness of corrective actions;
- complaints and appeals;
- the adequacy of resources;
- any identified risks and mitigation measures; and
- opportunities for improvements.

11. Publications

- 11.1 The inspectorate should issue and maintain an up-to-date list of inspected and licensed facilities and organizations, including information on the outcome of inspections. This list may become publicly available in accordance with national legislation.
- 11.2 The inspectorate should ensure that other relevant publications, such as technical guides, GXP guidelines and regulatory requirements, are publicly available.

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Further reading

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6.2 Provisional guidelines on the inspection of pharmaceutical manufacturers

Annex 2, WHO Technical Report Series, 823, 1992

These guidelines are intended to promote harmonization of pharmaceutical inspection practices among WHO Member States. They are directed to government inspectors - particularly those operating within small national regulatory authorities (1) - to assist them in assessing manufacturers' compliance with good manufacturing practices (GMP) (2). They will also be of value to manufacturers themselves when engaged in self-inspection or audit.

They cover inspection of the production and control of final dosage forms of pharmaceutical products destined for human and veterinary use and of drug substances (active pharmaceutical ingredients or bulk drug substances) employed in their manufacture. Within the national context their scope may need to be extended since similar regulations are often enforced to control pharmaceutical and biological products, medical devices, diagnostic products, foods, and food additives. In all cases the same fundamental principles apply.

Inspection and licensing of pharmaceutical manufacturing facilities on the basis of compliance with GMP are a vital element of drug control. They are also pivotal to the operation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce (3), which requires an attestation by the competent regulatory authority in the exporting country that a given product is manufactured in premises and using operating practices that conform with GMP.

The guidelines also have relevance in various other contexts, including:

- self-inspection or internal audit of a factory or a part of it carried out by personnel of the company;
- inspection by an independent person or group of persons as a review of the quality system of a company in compliance with the standards issued by the International Organization for Standardization (ISO 9000-9004 (4)) or the British Standards Institution (BS 57 50 (5)) or with other equivalent national standards;
- audit of a manufacturer or supplier by authorized agents of the customer.

The government inspectorate represents the enforcement arm of the national drug regulatory authority. Its function is to ensure adherence by manufacturers to all licensing provisions and specifically to GMP. The objectives are to control and enforce

general standards of production and to provide authorization for the manufacture of specific pharmaceutical products. The first objective involves a sequential examination of production and control activities on the basis of the GMP guidelines issued by WHO or of nationally determined requirements. The second requires verification that production and quality control procedures employed in the manufacture of specific products are performed correctly and that they accord with data supplied in the relevant licensing applications.

Inspection will, of course, depend on national legislation and regulations and/or the resources available.

The role of the inspector

Inspectors should have previous training and practical experience in the manufacture and/or quality control of pharmaceutical products. Graduate pharmacists, chemists, or scientists with an industrial background in pharmaceutical production would qualify for consideration.

In-post training should include an element of apprenticeship gained by accompanying experienced inspectors on site visits as well as participation in courses and seminars on relevant subjects including modern pharmaceutical technology, microbiology, and the statistical aspects of quality control.

The primary responsibility of an inspector is to present a detailed factual report on standards of manufacture and control applied to specific products. However, inspection should not be limited to compilation of an inventory of faults, irregularities, and discrepancies. Provided it is in keeping with national policy and does not breach understandings regarding confidentiality of information having commercial value, advice may be offered on how production and control procedures can be usefully upgraded. An inspector should always be expected, for example, to offer advice on how to improve an in-process test procedure or to offer other assistance which, in his or her opinion, serves the public interest. An inspection should be regarded as an opportunity to assist and motivate a manufacturer to comply with GMP and to correct any specific deficiencies.

The inspection process

The planning, organization, method of work, and format of the resultant report should always be determined by the precise objective of the inspection. Inspections vary in nature according to the objective:

Routine inspection

This is a full inspection of all applicable components of GMP and licensing provisions. It may be indicated when the manufacturer:

- is newly established;
- requests renewal of a licence to operate;
- has introduced new product lines or new products, or has made significant modifications to manufacturing methods or processes, or has made changes in key personnel, premises, equipment, etc.;
- has a history of non-compliance with GMP;
- has not been inspected during the last 3-5 years.

Concise inspection

Manufacturers with a consistent record of compliance with GMP through previous routine inspections are eligible for concise inspection. The focus of a concise inspection is on a limited number of GMP requirements selected as indicators of overall GMP performance, plus the identification of any significant changes that could have been introduced since the last inspection. Collectively, the information obtained will indicate the overall attitude of the firm towards GMP. Evidence of unsatisfactory GMP performance observed during a concise inspection should trigger a more comprehensive inspection.

Follow-up inspection (reassessment or reinspection)

Follow-up visits are made to monitor the result of corrective actions. They are normally carried out from 6 weeks to 6 months after the initial inspection, depending on the nature of the defects and the work to be undertaken. They are limited to specific GMP requirements that have not been observed or that have been inadequately implemented.

Special inspection

Special visits may be necessary to undertake spot checks following complaints or recalls related to suspected quality defects in products. Reports of adverse drug reactions may also indicate that all is not well. Such inspections may be focused on one product, a group of related products, or specific operations such as mixing, sterilization, or labelling.

Special visits may also be made to establish how a specific product is manufactured as a prerequisite for marketing approval or issuance of an export certificate.

A further reason for special visits is to gather specific information on - or to investigate - specific operations and to advise the manufacturer of regulatory requirements.

Quality systems review

A quality systems review is a relatively new concept. Its purpose is to describe a quality assurance system that has been shown to operate satisfactorily. It entails a description of the quality system and the standards to be observed, normally in a manual containing

a statement of the manufacturer's policy on quality assurance. It should also define the management structure needed to implement the policy, along with the procedures in each management area needed to ensure that adequate quality standards are set for the product, manufacturing processes are correctly defined, records are kept, and quality control and other quality assurance activities are carried out.

Frequency and duration of inspections

The frequency and duration of visits should be determined by the type of inspection required as well as by the workload and number of inspectors. New manufacturing establishments must be inspected before they are licenced, and new facilities must be inspected before production is started.

For all companies, inspections should be carried out on a regular schedule, ideally annually.

For large companies marketing a wide range of products, the inspection of the site may be split up into several visits over a longer period, e.g., 5 years where this is the period of validity of the manufacturing licence or the GMP certificates.

The length of a given inspection is determined by the size of the company and the purpose of the visit. It can extend from a few days to 2 weeks or more. The time taken also depends on the number of inspectors assigned to the visit. In many countries, visits are made by one (or more) inspectors, sometimes accompanied by a specialist when production of biologicals, sterile production areas, or other special facilities are to be examined.

Preparing for the inspection

Drug inspection begins at the desk of the inspector. A review should be made of the documents relating to the company to be visited, available from the drug regulatory authority. These may include the manufacturing licence, the marketing authorization dossiers for leading products, reports of adverse drug reactions, complaints and recall records, the results of regulatory (surveillance) testing, and the previous inspection reports.

Company documents, including the annual report for the shareholders, the complaints file, and self-inspection/internal audit reports, are valuable sources of information. The last of these, depending on national legislation, may be withheld from the inspector. In some countries, a compromise is reached, the company presenting the internal audit reports to the inspector for general information after the latter's own report has been finalized. In any case, it should be possible to verify the frequency of self-inspections, and to which parts of the plant they have been applied.

Conduct

Announced inspections cover regular visits to evaluate new plants and new production lines and to decide on the renewal of a licence.

Unannounced inspections are necessary for concise, follow-up, and special visits. In certain countries regular inspections are unannounced as a matter of policy.

The visit usually begins with a meeting between the inspector(s), representatives of the company or plant management, and those responsible for the products or areas to be inspected. Credentials should be presented, letters of authority inspected, and an explanation given of why the inspection is being carried out.

It is advantageous for the company to appoint at least one “escort” who is directly involved in the preparation of the products that are the object of the inspection. Escorts should be chosen who are generally familiar with the quality systems of the company and who are involved in the self-inspection programme.

The meeting may be followed by a perusal of the company’s documents by the inspector or by a walk-through visit, or both. This will permit the inspector to finalize the plan for the inspection. It is recommended that the inspector both develops and follows this plan independently, rather than accepting guidance from company management. Some basic rules for conducting the inspection are as follows:

- Inspection should follow the original plan as far as possible; items that are specific to certain areas of the facility, such as in-process testing and working documents, may need to be checked at the point of operation. Care should be taken to cover activities such as water production, sample storage, and validation.
- It is advisable to follow production flow from reception of the starting materials to the shipment of the finished products. The frequency of recalls and return of goods should be carefully noted.
- Documents such as master formulae, test specifications, standard operating procedures, and batch records (including protocols of analyses, etc. and documents relating to the control of printed materials and labelling operations) require close verification.

Without prejudice to the need to verify documentation, it is essential that the inspection be based largely on observation and cover the total working hours of the manufacturer. It is recommended that the inspector start the plant tour as soon as possible after arrival.

Inspectors can profitably use a short checklist to ensure that all areas of operations have been investigated. A very detailed checklist developed from GMP guidelines is of use specifically for the training of inspectors. Experience has shown that rigid adherence to a too-detailed checklist can lead to possible overlooking of vulnerable areas of a quality assurance system specific to the company/plant under investigation. For an experienced inspector, knowledge of the manufacturer’s weak points allied with intuition may serve better than a checklist. Different checklists may be found in the recommended publications and documents listed in Appendix 1.

Stability-testing programme. The inspector should be satisfied that there exists a documented ongoing programme specifying the regular withdrawal of samples of all products from the production line for stability testing. The testing schedule for stored samples should employ appropriate conditions of temperature and light stress, and suitable stability-indicating analytical methods that yield conclusions consistent with claimed shelf-life. The systems should permit re-evaluation of product stability following any changes in the manufacturing process or formula.

Significant changes in facilities, equipment, products, and senior personnel since the last inspection should be noted. The principle here is that changes represent possible areas of weakness or causes of non-compliance with GMP. For example, new equipment may require changes to be made in procedures; new product lines may require new product master files; and departures of senior personnel such as the quality control manager may result in behavioral or procedural changes.

Occasionally, an inspector may require access to other premises, documents, or information on the company. Ideally, the inspector's authority should be determined by legislation, but in the absence of clear legal or regulatory provisions, it is suggested that the GMP code is used as a guide and the inspector should have the right to verify compliance with every requirement listed in the code.

The inspector should not be concerned about information not covered by GMP - e.g., finance and personnel - where this does not infringe on the company's responsibilities or staff education and training.

Photographs or videos taken during the visit may be excellent illustrative material for the report. National legislation should stipulate that the inspector has the right to take visual records during the inspection to document the production premises or laboratories.

In many cases, an aerial photograph of the manufacturing site, possibly with surrounding grounds, may be obtained from the company together with other relevant materials for inclusion in the report.

Collecting samples. It is normal practice during the visit for the inspector to take samples for testing by the official quality control laboratory. Samples are usually taken from released products (e.g., from the finished-goods warehouse) but may also be taken from stocks of raw materials or in-process material. In order to protect sample integrity, any protocol meant for enforcement or legal purposes should set out the procedures for sample collection, analysis, and documentation. The following should be stated:

- name(s) of the sampled product(s), batch number(s), date, source, number of samples, and remarks on type of packaging and storage conditions;
- circumstances of sampling, e.g., suspected quality defects, routine surveillance, verification of compliance with GMP;
- instructions for the placing of seals on containers of sample materials;
- written confirmation of the receipt of the samples by the inspector (possibly together with the manufacturer's certificates of analysis and any other supporting documents).

The manufacturer, represented by the company escort, should be encouraged to take duplicate samples from the same batch(es), for “in-house” testing if a problem is later identified.

Before the inspector leaves the premises after the inspection, a final discussion with company management is recommended. If possible, the inspector should list any unsatisfactory findings and outline any irregularities or other observations to which management may wish to respond.

Report

It is recommended that reports be divided into four parts: general information on the company or manufacturing facility, description of the inspection, observations, and conclusions. Annexes may contain supporting information (a list of products manufactured, an organization chart, the annual company report, photographs, etc.). The third and fourth parts may be combined. Appendix 2, which is an extract from a document prepared for the Pharmaceutical Inspection Convention, provides an example of the form and content of the inspector’s report.

In order to save the inspector’s time, the first part of the report containing basic data may be supplied by the company beforehand, provided that this fact is clearly stated in the report and the information supplied is verified by the inspector during the visit. An example of items that should be considered for inclusion is given in Appendix 2, section C “Site master file”.

The second part should describe the complete progress of the inspection step by step, documenting which parts of the factory, warehouses, laboratories, records, documents, etc. were inspected.

The third part is devoted to observations. Changes, improvements, and examples of deterioration since the previous inspection should be noted by the inspector.

Positive observations should take the form of a description of the processes that the firm is carrying out particularly well and that may be considered examples of particularly good manufacturing practice.

Negative observations (non-compliance with GMP requirements) should distinguish between whether the defect lies in the system itself or in a failure to comply with the system. For instance, when cleaning is found to be suboptimal, it is important to know whether the standard operating procedures are inadequate or lacking, or whether adequate written procedures exist but are not being followed by personnel.

In the final part of the report, the inspector should summarize deficiencies, unsatisfactory practices, etc. (listed in decreasing order of importance), suggest corrective actions, and make recommendations. This part, together with the third part, should be discussed with the company management and responsible authorized persons at the end of the inspection.

A copy of the complete written report, after supervisory approval, should be provided to the company management with a covering letter. The corrective actions to

be taken, together with a time limit for their execution, should also be presented to the management of the company.

Inspection reports may be treated as confidential documents depending on national legislation. Under certain international agreements, reports may be exchanged between drug regulatory authorities.

Regulatory actions

Depending on national legislation, regulatory authorities may take action to correct unsatisfactory practices and prevent the distribution of products with suspected quality defects or manufactured under conditions that do not comply with GMP requirements. In extreme cases, the closing down of operations may be required. In practice, these measures are used only in exceptional cases constituting a hazard to health.

In many countries, the drug regulatory authority has the legal power to suspend or revoke the marketing authorization for a product when the manufacturer does not comply with GMP. In addition, manufacturing or marketing authorizations (licences), the reregistration of products, and the issue of a variation licence or a GMP certificate may be delayed until appropriate measures have been taken by the company, and possibly have been confirmed by reinspection. As a rule, the manufacturer concerned has the right to appeal.

References

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4. *International Standards: Quality management and quality assurance standards - Guidelines for selection and use (ISO 9000); Quality systems - Model for quality assurance in design/development, production, installation and servicing (ISO 9001); Quality systems - Model for quality assurance in production and installation (ISO 9002); Quality systems - Model for quality assurance in final inspection and test (ISO 9003); Quality management and quality system elements - Guidelines (ISO 9004)*. Geneva, International Organization for Standardization, 1987 (rev. 1990).
5. *Quality systems. Part 2. Specification for manufacture and installation (BS 5750: Part 2)*. London, British Standards Institution, 1979.

Appendix 1

Recommended publications and documents

- ASEAN manual for inspection of GMP. Association of South East Asian Nations, 1988.
- Drug manufacturer's self-inspection manual as to conformity with GMP requirements. In: *GMP regulations of Japan*, 3rd ed. Tokyo, Ministry of Health and Welfare, 1988: 101-195.
- Good drug manufacturing practices (GMP), audit check-list. Government of Brazil, Ministry of Health, 1983.
- Grundregeln für die Herstellung von Wirkstoffen und die Sicherung ihrer Qualität; Fragebogen zu den Grundregeln für die Herstellung von Wirkstoffen und die Sicherung ihrer Qualität [Basic rules for the production of active ingredients and their quality assurance; audit checklist to the basic rules for the production of active ingredients and their quality assurance]. *Pharmazeutische Industrie*, 1981, 43: 537-542 (republished in : Oeser W, Sander A. *Pharma-Betriebsverordnung, Kommentar [GMP comments]*. Stuttgart, Wissenschaftliche Verlagsgesellschaft, 1988).
- Guide to inspection of bulk pharmaceutical chemical manufacturing. Food and Drug Administration, US Department of Health and Human Services, Public Health Service, 1987.
- Steinborn L. Quality assurance manual for the pharmaceutical and medical device industries. Buffalo Grove, IL, Interpharm Press, 1986.

Appendix 2

Form and content of the inspector's report¹

A. Inspector's information

1. Date of inspection(s) on which the information is based and name(s) of inspector(s).
2. Brief report of inspection activities undertaken.
3. Samples taken and results obtained.
4. Assessment of the site master file (see section C).
5. GMP-related recalls from the market of any product in the last two years.

B. Summary and conclusions

1. The inspector's general impression of the firm and his or her assessment of the acceptability of its GMP status for the range of products concerned.
2. Failures to comply with the PIC Guide to Good Manufacturing Practice (in order of importance) and with the time limits set for them to be corrected by the manufacturer.

C. Site master file

A site master file is a document prepared by the manufacturer containing specific and factual GMP information about the production and/or control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of a pharmaceutical operation is carried out on the site, the site master file need describe only those operations, e.g., analysis, packaging.

A site master file should be succinct and, as far as possible, not exceed 25 A4 pages.

¹ Extracted (with permission and minor changes) from an unpublished document (PH 6/91) prepared for the Pharmaceutical Inspection Convention, November 1991.

1. General information

- 1.1 Brief information on the firm (including name and address), relation to other sites, and in particular, any information relevant to understanding the manufacturing operations.
- 1.2 Pharmaceutical manufacturing activities as licensed by the national authority.
- 1.3 Any other manufacturing activities carried out on the site.
- 1.4 Name and exact address of the site, including telephone, fax, and 24-hour telephone numbers.
- 1.5 Type of products manufactured on the site, and information about any specifically toxic or hazardous substances handled, mentioning the way they are manufactured (in dedicated facilities or on a campaign basis).
- 1.6 Short description of the site (size, location, and immediate environment and other manufacturing activities on the site).
- 1.7 Number of employees engaged in production, quality control, storage, and distribution.
- 1.8 Use of outside scientific, analytical, or other technical assistance in relation to manufacture and analysis.
- 1.9 Short description of the quality management system of the firm responsible for manufacture.

2. Personnel

- 2.1 Organization chart showing the arrangements for quality assurance, including production and quality control.
- 2.2 Qualifications, experience, and responsibilities of key personnel.
- 2.3 Outline of arrangements for basic and in-service training and how records are maintained.
- 2.4 Health requirements for personnel engaged in production.
- 2.5 Personnel hygiene requirements, including clothing.

3. Premises and equipment

Premises

- 3.1 Simple plan or description of manufacturing areas with indication of scale (architectural or engineering drawings not required).
- 3.2 Nature of construction and finishes.
- 3.3 Brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination (schematic drawings of the systems are desirable). Classification of the rooms used for the manufacture of sterile products should be mentioned.
- 3.4 Special areas for the handling of highly toxic, hazardous, and sensitizing materials.
- 3.5 Brief description of water systems (schematic drawings of the systems are desirable), including sanitation.
- 3.6 Description of planned preventive maintenance programmes for premises and of the recording system.

Equipment

- 3.7 Brief description of major equipment used in production and control laboratories (a list of equipment is not required).
- 3.8 Description of planned preventive maintenance programmes for equipment and of the recording system.
- 3.9 Qualification and calibration, including the recording system. Arrangements for computerized systems validation.

Sanitation

- 3.10 Availability of written specifications and procedures for cleaning manufacturing areas and equipment.

4. Documentation

- 4.1 Arrangements for the preparation, revision, and distribution of necessary documentation for manufacture.
- 4.2 Any other documentation related to product quality that is not mentioned elsewhere (e.g., microbiological controls on air and water).

5. Production

- 5.1 Brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters.
- 5.2 Arrangements for the handling of starting materials, packaging materials, and bulk and finished products, including sampling, quarantine, release, and storage.
- 5.3 Arrangements for the handling of rejected materials and products.
- 5.4 Brief description of general policy for process validation.

6. Quality control

- 6.1 Description of the quality control system and of the activities of the quality control department. Procedures for the release of finished products.

7. Contract manufacture and analysis

- 7.1 Description of the way in which the GMP compliance of the contract accepter is assessed.

8. Distribution, complaints, and product recall

- 8.1 Arrangements and recording system for distribution.
- 8.2 Arrangements for the handling of complaints and product recalls.

9. Self-inspection

- 9.1 Short description of the self-inspection system.

6.3 Guidance on good manufacturing practices: inspection report

Annex 4, WHO Technical Report Series, 996,
2016

Background

The need for revision of the *Guidance on good manufacturing practices: inspection report* (World Health Organization (WHO) Technical Report Series, No. 908, Annex 6, 2003) was brought to the attention of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The intent of this update is to bring it in line with the current format used by the Prequalification Team (PQT) for its inspections and the formats currently used internationally in national and regional inspectorates. In addition, the concepts of risk management, as, for example, included in the *WHO guidelines on quality risk management* (WHO Technical Report Series, No. 986, Annex 6, 2014), have been taken into consideration.

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1. Introduction

- 1.1 This guidance describes general principles and a recommended format for inspection reports for use by organizations performing pharmaceutical inspections. It aims to support convergence of practices in drawing up inspection reports so as to facilitate cooperation and information sharing.

2. Scope

- 2.1 These guidelines apply to reports on inspections of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs). A separate template may be used for inspections of contract research organizations and quality control laboratories.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

correction. A correction is any action that is taken to eliminate a nonconformity. However, corrections do not address causes. When applied to products, corrections can include reworking products, reprocessing them, regrading them, assigning them to a different use, or simply destroying them.

corrective action. Corrective actions are steps that are taken to eliminate the causes of existing nonconformities in order to prevent recurrence. The corrective action process tries to make sure that existing nonconformities and potentially undesirable situations do not happen again. While corrective actions prevent recurrence, preventive actions prevent occurrence. Both types of actions are intended to prevent nonconformities.

corrective and preventive action. A system for implementing corrective actions and preventive actions resulting from an investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring.

deficiency. Non-fulfilment of a requirement. In this sense this term can be used interchangeably with “nonconformity”.

inspection observation. An inspection observation is a finding or a statement of fact made during an inspection and substantiated by objective evidence. Such findings may be positive or negative. Positive observations should take the form of a description of the processes that the firm is carrying out particularly well and that may be considered examples of particularly good practice. Negative observations are findings of non-compliance with requirements.

nonconformity. Nonconformity refers to a failure to comply with requirements. A requirement is a need, expectation or obligation. It can be stated or implied by an organization, its customers or other interested parties. There are many types of requirements. These include quality requirements, customer requirements, management requirements, product requirements, process requirements and legal requirements. Whenever an organization fails to meet one of these requirements, a nonconformity occurs.

preventive action. Preventive actions are steps that are taken to remove the causes of potential nonconformities or potential situations that are undesirable.

4. General principles

- 4.1 When a site at which pharmaceutical products are manufactured is inspected, the inspector(s) responsible should draw up a report. The inspection report should include the items shown in the proposed model inspection report (Appendix 1), adapted as appropriate, according to the national or regional settings and to the scope and purpose of the inspection. Where relevant the appropriate system of good manufacturing practices (GMP) or the nationally appropriate legal basis for GMP, should be indicated.
- 4.2 The purpose of an inspection report is to provide a factual and objective record of the inspection that includes what was done, the inspection observations or findings (positive and negative) for each activity inspected, as communicated to the company before the end of the inspection, and a conclusion that is applicable at the time that the report is written. Positive findings may include praise for noteworthy efforts in areas that are seen as excellent examples of implementation of the requirements of the guidelines. They could also be conveyed when the company has shown significant improvement in certain areas compared to the findings from previous inspections. Noteworthy efforts do not require any action. Their inclusion in the inspection report is done to highlight areas of strength for future tracking of improvements or areas of decline and to show the organization what areas it can feel proud of.
- 4.3 The report should be prepared in a timely manner after an inspection, with the participation of all members of the inspection team under the coordination of the lead inspector. The report should be reviewed in accordance with the quality system of the inspectorate.
- 4.4 The inspection report should, as appropriate, be written in the third person, passive voice and the past tense.

Example: “Cleaning logs for rooms and equipment were maintained in all areas of the factory.”

- 4.5 All the observations that are considered as deficiencies/noncompliances should be listed under Part 3 of the report. Each observation included in an inspection report should be referenced to the relevant GMP text, WHO guidelines or conditions or commitments under the marketing authorization. An observation that cannot be reasonably referenced should not be listed as a deficiency.
- 4.6 The non-compliance statement should include the requirement (R), evidence (E) and deficiency (D).

Example: (R) The relevant cleaning records and source data should be kept in cleaning validation reports; (E) the source of three samples taken for recovery testing during the process equipment validation was not traceable; (D) cleaning validation reports did not include sufficient data.

- 4.7 Deficiencies/noncompliance statements should distinguish whether the defect lies in the system itself or in a failure to comply with the system. For instance, when cleaning is found to be suboptimal, it is important to know whether the standard operating procedures (SOPs) are inadequate or lacking, or whether adequate written procedures exist but are not being followed by personnel.
- 4.8 Where more than one deficiency relates to the same basic quality system failure, the deficiencies should be grouped and listed as a single observation, under a heading that reflects the basic system failure.
- 4.9 Deficiencies should be reported with a focus on risk to patient health and/or need for corrective and preventive action (CAPA).
- 4.10 The report should not include comments that could be construed as proposed specific solutions to issues raised. Recommendations should relate to recommended regulatory action as appropriate.
- 4.11 Each deficiency should be classified as critical, major or other, according to the following definitions, which may be adapted according to the national or regional legal context.
 - 4.11.1 A *critical* deficiency may be defined as an observation that has produced, or may result in a significant risk of producing, a product that is harmful to the user.
 - 4.11.2 A *major* deficiency may be defined as a non-critical observation that:
 - a) has produced or may produce a product that does not comply with its marketing authorization and/or prequalification application (including variations);
 - b) indicates a major deviation from the GMP guide;

- c) indicates a failure to carry out satisfactory procedures for release of batches;
- d) indicates a failure of the person responsible for quality assurance/quality control to fulfil his or her duties;
- e) consists of several other deficiencies, none of which on its own may be major, but which together may represent a major deficiency and should be explained and reported as such.

4.11.3 A deficiency may be classified as *other* if it cannot be classified as either *critical* or *major*, but indicates a departure from GMP. A deficiency may be *other* either because it is judged as minor or because there is insufficient information to classify it as *major* or *critical*.

4.11.4 Classification of a deficiency is based on the assessed risk level and may vary depending on the nature of the products manufactured, e.g. in some circumstances an example of an *other* deficiency may be categorized as *major*.

4.11.5 A deficiency that was reported at a previous inspection and was not corrected may be reported with a higher classification.

4.11.6 One-off minor lapses or less significant issues are usually not formally reported, but are brought to the attention of the manufacturer during the inspection.

4.11.7 The status of compliance with WHO GMP guidelines should be determined by the nature and number of deficiencies:

- a) When there are *other* deficiencies only:
 - i. the site is considered to be operating at an acceptable level of GMP compliance,
 - ii. the manufacturer is expected to provide CAPAs,
 - iii. CAPAs are evaluated and followed up during the next routine inspection.
- b) When there are *other* and a few *major* deficiencies (e.g. < 6¹):
 - i. the site is compliant with GMP after assessing the CAPAs,
 - ii. CAPAs for *all* deficiencies to include actions implemented and/or planned, timelines and documented evidence of completion, as appropriate,
 - iii. CAPAs are evaluated on paper and may or may not include an on-site, follow-up inspection.

¹ The number six is related to the six systems to be inspected, as listed in Appendix 1.

- c) When there are *critical* or several *major* deficiencies (e.g. ≥ 6):
 - i. the site is considered to be operating at an unacceptable level of compliance with GMP guidelines,
 - ii. another inspection will normally be required,
 - iii. administrative and/or legal enforcement actions are applied as necessary.
- 4.12 The next date for inspection of the site should be determined depending on the level of compliance and risk category as defined under national or regional procedures. Appendix 2 provides an example of how the next inspection date may be determined. Other approaches may be used.
- 4.13 The report shall be signed by all inspection team members, but may be signed by the lead inspector after consultation with and on behalf of the inspection team, and reviewed in accordance with the quality system of the inspectorate.

Appendix 1

Guidance on good manufacturing practices: inspection report

Model inspection report

Part 1		General information
Manufacturer details		
Company	Name of manufacturer Corporate address of manufacturer (including telephone, fax, email and 24-hour telephone numbers) Contact person, telephone number and email address	
information	Address of inspected manufacturing site if different from that given above (including global positioning system (GPS) coordinates in World Geodetic System (WGS) 84: latitude and longitude expressed in decimal degrees, taken at the main entrance of the site; data universal numbering system (D-U-N-S) number: NNNNNNNNNN, where each N represents a number from 0–9, if available) and specific production blocks or workshops inspected if the whole site was not inspected Site number (e.g. unit number, site master file number or number allocated by the responsible authority) Manufacturing licence number (if applicable) Key personnel	
Summary of activities performed at the site	For example, manufacture of active pharmaceutical ingredient(s) (APIs), manufacture of finished pharmaceutical products (FPPs), intermediates or bulk packaging, laboratory testing, batch release, distribution and importer activities	
Inspection details		
Date(s) of inspection(s)	...	
Type of inspection	For example, initial, routine, follow-up, special	
Inspector(s)	Name(s) and agency affiliations of lead inspector, inspector(s), accompanying experts and observers	

Table continued

Part 1	General information
Competent regulatory authority	For foreign inspections, state whether the national regulatory authority (NRA) of the country where the inspection took place was informed and whether it took part in the inspection
GMP guidelines used for assessing compliance	<p>List the relevant guidelines stating the title of the guidelines, the title of the publication and web address where the guidelines can be accessed, for example:</p> <ol style="list-style-type: none"> WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986; http://www.who.int/entity/medicines/areas/quality_safety/quality_assurance/TRS986annex2.pdf?ua=1)
Introduction	
Brief summary of the manufacturing activities	<p>Description of main activities (including, e.g. FPP(s) or API(s) manufactured and their reference/registration/active pharmaceutical ingredient master file (APIMF)/drug master file (DMF)/certificate of suitability to the monographs of the European Pharmacopoeia (CEP) numbers, as appropriate); other manufacturing activities carried out on the site (e.g. manufacture of cosmetics, research and development); use of outside scientific, analytical or other technical assistance in manufacture and quality control</p> <p>Brief description of the quality management system of the firm responsible for manufacture. Reference can be made to a site master file if one is available</p>
History	<p>Previous inspection date and history of regulatory agency inspections</p> <p>Summary of past inspections; observations on CAPA from previous inspection</p> <p>Major change since previous inspection and planned future changes</p> <p>GMP-related recalls from the market of any product in the past two years</p>

Table *continued*

Part 1	General information
Brief report of inspection activities undertaken	
Scope and limitations	For example, blocks inspected, areas of interest, focus of inspection Out-of-scope: areas, activities or product lines not inspected Restrictions: constraints noted in inspecting specific areas
Areas inspected	For example, dosage form(s) included in the inspection
Key persons met	Names and job titles
Part 2	Brief summary of the findings and recommendations (where applicable)
	<p>This part of the report is arranged based on the WHO Guidance for good manufacturing practices: main principles. It may also be arranged according to six inspection systems, namely:</p> <ol style="list-style-type: none"> 1. pharmaceutical quality system, 2. production system, 3. facilities and equipment system, 4. laboratory control system, 5. materials system, 6. packaging and labelling system. <p>The observations made during the inspection that are considered to be non-compliant with GMP should be listed. Where positive observations are included in the report, a clear distinction should be made between positive and non-compliant.</p> <p>Non-compliant observations can be classified, e.g. as <i>critical</i>, <i>major</i> and <i>other</i> if the Member State concerned has defined these terms</p> <p>The date by which corrective action and completion are requested in accordance with the policy of the NRA should be given.</p>
1. Pharmaceutical quality system	Describe the pharmaceutical quality system (PQS) in place and how well the elements are institutionalized and implemented, including the quality risk management (QRM) and product quality review (PQR)

Table continued

Part 2	Brief summary of the findings and recommendations (where applicable)
2. Good manufacturing practices for pharmaceutical products	Briefly describe how the elements of GMP are implemented
3. Sanitation and hygiene	Describe procedures and records relating to sanitation and hygiene for personnel, premises, equipment, production materials, cleaning materials and others that could become a source of contamination
4. Qualification and validation	Describe policies, procedures, records and any other evidence for qualification and validation and how the validation status is monitored and maintained
5. Complaints	Describe procedures, responsibilities and records for handling complaints, including extension of investigation to other batches, possibility of counterfeits, trending and consideration for recall and notification of competent authorities
6. Product recalls	Describe the existence of a recall procedure and evidence of its effectiveness; provisions for notification of customers and competent authorities and segregation of recalled products
7. Contract production, analysis and other activities	Describe how contractors are evaluated, how compliance with marketing authorization is ensured, existence of comprehensive contracts and clarity of responsibilities and limits
8. Self-inspection, quality audits and suppliers' audits and approval	<p>a) Self-inspection: describe the procedures and items for self-inspection and quality audits; constitution of self-inspection team(s); frequency of self-inspection; existence of self-inspection schedules and report; system for monitoring follow-up actions.</p> <p>b) Suppliers' audits and approval: describe procedures for evaluation and approval of suppliers including applications of risk management principles, especially determining the need and frequency for on-site audits.</p>

Table continued

Part 2	Brief summary of the findings and recommendations (where applicable)
9. Personnel	Describe availability of adequate numbers of sufficiently qualified and experienced personnel, clarity of their responsibilities, limits and reporting hierarchy. Qualifications, experience and responsibilities of key personnel (head of production, head(s) of the quality unit(s), authorized person) and procedures for delegation of their responsibilities
10. Training	Describe comprehensiveness of procedures and records for induction, specialized and continuing training and evaluation of its effectiveness; coverage of GMP and concepts of quality assurance during training; training of visitors and evaluation consultants and contract staff
11. Personal hygiene	Describe system in place for initial and regular health examination of staff appropriate to their responsibilities. Measures and facilities to impart, maintain and monitor knowledge of a high level of personal hygiene. Measures to ensure personnel do not become a source of contamination to the product, including hand-washing and gowning. Appropriate restriction of smoking, eating, drinking, chewing and related materials from production, laboratory and storage areas
12. Premises	Description of the appropriateness of the location, design, construction and maintenance of premises to minimize errors, avoid cross-contamination, permit effective cleaning and maintenance; measures for dust control; specific measures for ancillary areas, storage areas, weighing areas, production areas and quality control areas; measures for appropriate segregation and restricted access; provisions for appropriate lighting, effective ventilation and air-control to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity
13. Equipment	Describe the adequacy of the numbers, type, location, design and construction, and maintenance of equipment to minimize errors, avoid cross-contamination, permit effective cleaning and maintenance; use, cleaning and maintenance procedures, records and logs; calibration of balances and other measuring instruments; status labelling

Table continued

Part 2	Brief summary of the findings and recommendations (where applicable)
14. Materials	Describe measures in place to select, store, approve and use materials (including water) of appropriate quality and how these measures cover starting materials, packaging materials, intermediate and bulk products, finished products, reagents, culture media and reference standards. Describe also the measures for the handling and control of rejected, recovered, reprocessed and reworked materials; recalled products; returned goods; and waste materials
15. Documentation	Describe the comprehensiveness and adequacy of the documentation system in place (labels; specifications and testing procedures, starting, packaging materials, intermediate, bulk products and finished products; master formulas; packaging instructions; batch processing and packaging records; standard operating procedures (SOPs) and records) and how principles of good documentation and data management (attributable, legible, contemporaneous, original, accurate (ALCOA)) are institutionalized, implemented and maintained
16. Good practices in production	Describe procedures, facilities and controls in place for production (processing and packaging); prevention of risk of mix-up, cross-contamination and bacterial contamination during production
17. Good practices in quality control	<p>Describe the extent of the organizational and functional independence of the quality control function and the adequacy of its resourcing.</p> <p>Describe the procedures, facilities, organization and documentation in place which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be compliant with the requirements.</p> <p>Describe the procedures for the control of starting materials and intermediate, bulk and finished products; test requirements; procedures and responsibilities for batch record review; procedures, records and facilities for initial and ongoing stability studies; policy, procedures, facilities and records for retention samples.</p>

Table *continued*

Part 2	Brief summary of the findings and recommendations (where applicable)	
Samples taken	(if applicable)	
Assessment of the site master file	(if applicable)	
Annexes attached	...	
Part 3	List of deficiencies	
List of deficiencies	Deficiencies should be listed by category with reference to the relevant section(s) of GMP guidelines. This may be presented in a tabular format, giving references to the relevant GMP requirement:	
	Deficiencies	References
1. Critical	1.1 ... 1.2
2. Major	2.1 ... 2.2
3. Other	3.1 ... 3.2
Part 4	Outcome	
List of deficiencies	<p>Statement regarding the GMP status, including information on any restrictions in scope.</p> <p>The following guidance may be used to determine the outcome of the inspection based on the nature and number of deficiencies observed:</p> <ul style="list-style-type: none"> • <i>other</i> deficiencies only: operating at an acceptable level of compliance with GMP guidelines; • <i>other</i> and a few (e.g. < 6) <i>major</i> deficiencies: decision on level of compliance to be made after receipt and evaluation of CAPAs; • <i>any critical</i> or several (e.g. ≥ 6) <i>major</i> deficiencies: operating at an unacceptable level of compliance with GMP guidelines. 	

Part 5	List of GMP guidelines referenced in the inspection
References	<p>List of GMP guidelines referred to in the inspection, for example:</p> <ol style="list-style-type: none"> 1. WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986; http://www.who.int/medicines/publications/pharmprep/en/index.html) 2. WHO good manufacturing practices for sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 6 (WHO Technical Report Series, No. 961; http://www.who.int/medicines/publications/pharmprep/en/index.html) 3. WHO good manufacturing practices for active pharmaceutical ingredients. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 3 (WHO Technical Report Series, No. 957; http://www.who.int/medicines/publications/pharmprep/en/index.html) 4. WHO good manufacturing practices: water for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-sixth report. Geneva: World Health Organization; 2012: Annex 2 (WHO Technical Report Series, No. 970; http://www.who.int/medicines/publications/pharmprep/en/index.html) 5. WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 5 (WHO Technical Report Series, No. 961; http://www.who.int/medicines/publications/pharmprep/en/index.html) 6. General guidelines for the establishment maintenance and distribution of chemical reference substances. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-first report. Geneva: World Health Organization; 2011: Annex 3 (WHO Technical Report Series, No. 937; http://www.who.int/medicines/publications/pharmprep/en/index.html)

Part 6	Assessment of company response, final conclusion, risk rating and next due date
Brief narrative on the adequacy of the company's response to issues to be addressed	...
Final conclusion	Final statement of GMP compliance, including information on any restrictions in scope
Risk rating following the inspection	For example, low (L), medium (M), high (H), critical (C)
Date next inspection due (for planning purposes)	The inspectorate may decide to include this information for internal use only
Name(s) (all inspectors or lead inspector)	
Signature(s) (all inspectors or lead inspector)	
Date	

Appendix 2

Example of a risk category assessment of the site depending on level of compliance and inspection frequency

Risk category of the site	GMP compliance rating and related inspection frequency (in months)			
	Acceptable			Unacceptable
	Good	Satisfactory	Basic	
Critical (C)	24	18	12	Determine on a case-by-case basis
High (H)	30	20	15	Determine on a case-by-case basis
Medium (M)	36	24	18	Determine on a case-by-case basis
Low (L)	48	36	24	Determine on a case-by-case basis

6.4 Guidelines on pre-approval inspections

Annex 7, WHO Technical Report Series, 902,
2002

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1. General

The advice provided here extends that given in the “Provisional guidelines on the inspection of pharmaceutical manufacturers” (1). The objectives of an inspection, as given in the introduction to the guidelines, are:

- to control and enforce compliance with general good manufacturing practices (GMP) (2); and
- to authorize the manufacture of specific pharmaceutical products, normally in response to a licensing application.

These guidelines are applicable mainly to inspections of the first type, whether performed as a condition for the issue of a manufacturing licence/authorization, or on a periodic, routine basis. They are essentially concerned with inspections of manufacturing and quality-control facilities conducted before a marketing authorization (product licence or registration) for a pharmaceutical product is granted.

2. Glossary

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

application

A marketing authorization for a new drug application.

manufacturer

A company that carries out at least one step of manufacture (2).

manufacture

All operations concerned with the purchase of materials and products, production (including packaging), quality control, release, storage, the distribution of pharmaceutical products, and the related controls (2).

method validation/verification

Method validation is conducted where non-compendial analytical methods are included in the application to confirm that the applicants' proposed analytical methods are suitable for regulatory purposes. A side-by-side comparison with a compendial method, if available, should be included. Method verification is conducted where the methods are compendial, to confirm whether the product as compounded can be analysed satisfactorily by the official method.

pre-approval batches

Pilot or laboratory-scale batches, upon which the application is based, e.g. batches used for pivotal clinical trials and/or those used for bioavailability, bioequivalence and stability studies, and scale-up batches.

3. Objectives

Before any application is approved, it is necessary to determine whether all establishments participating in the manufacture of the finished dosage form are in compliance with GMP and the application commitments. Pre-approval inspections have the following specific objectives:

- Evaluation of the establishment's compliance with GMP requirements, particularly regarding proper environment, quality management, personnel, facilities and equipment.
- Evaluation of the procedures and controls implemented in the manufacture of the product (pre-approval batches), to determine whether they are in conformity with the application commitments.
- Audit of the completeness and accuracy of the manufacturing and testing information submitted with the application, and of the conformity of pre-approval batches with planned commercial batches (process validation protocol).
- The collection of samples for the validation or verification of the analytical methods included in the application.

4. Priorities

Pre-approval inspections are considered to be an important part of the application review and approval process. However, since this represents a considerable workload, inspections are not normally carried out routinely, but rather only in specific cases where non-compliance is possible. Thus inspections may be required for:

- new chemical entities;
- drugs of narrow therapeutic range, and drugs for serious conditions requiring an assured therapeutic response;
- products previously associated with serious adverse effects, complaints, recalls, etc.;
- products that are difficult to manufacture or test, or that are of doubtful stability (and therefore associated with the risk of defects);
- new applicants or manufacturers; and

- applications from manufacturers who have previously failed to comply with GMP or official quality specifications.

For other applications, the drug regulatory authority will rely on the results of recent inspections of the applicant's or manufacturer's facilities for the production of dosage forms similar to that of the proposed product.

5. Preparation for the inspection

An inspection team should, where possible, include analysts and other specialists, e.g. in pharmaceutical technology, or if available, persons with expertise in these fields, when needed. Team members may be assigned to inspect new operations or manufacturing sites associated with product failures. When possible, the analyst involved in the laboratory evaluation of the product under review should participate in the inspection. Pre-approval inspection is often carried out by a single inspector.

It is necessary to verify that the applicant holds an appropriate manufacturing authorization and that manufacturing is carried out in conformity with that authorization (licence).

An essential step in the review of applications is determining whether the commitments made by the manufacturer are reflected in actual practice. A review of the application information is also important in preparing for inspections of firms or processes with which the inspector is unfamiliar. The drug regulatory authority should provide inspectors with relevant information on the application. (Some countries request an additional copy of this information from applicants which is forwarded to the inspection team.) The information provided should include a copy of the manufacturing and controls section of the application, together with information relating to pre-approval batches.

Reasonable efforts should be made to conduct pre-approval inspections at the earliest possible opportunity, since unnecessary delays will prevent the timely review of applications. However, in some facilities the development or the manufacturing processes may not have been completed. In addition, changes may have occurred in the status of the application, e.g. major deficiencies in the application or the closure of an ancillary facility may affect the need for an inspection. In any case, the timing of the inspection should be coordinated between the inspectorate and the applicant.

For the inspection of major new facilities involving many applications, special coordination efforts are often beneficial.

When desirable, pre-approval inspections should be coordinated with the laboratory scheduled for method validation so as to enable it to participate in the inspection and in the collection of samples.

6. Carrying out the inspection

Emphasis should be placed on the evaluation of the manufacturing process, including data verification and the assessment of compliance with GMP. The production and control procedures described in the application must be compared with those used for the manufacture of pre-approval batches. If warranted by records of past label mix-ups, packaging and labelling control procedures should be evaluated. A programme of ongoing stability testing needs to be addressed.

The inspection team will determine whether the application provides the scientific data justifying full-scale production procedures and controls. The validation of pertinent manufacturing procedures, including equipment qualification, will also be evaluated.¹ However, inspectors should not recommend withholding approval of applications based on a lack of complete full-scale, multiple-batch validation of sterile and non-sterile processes, unless the data submitted in the application are found to be of questionable validity or completeness. It should be understood that full-scale validation may be completed after approval of the application, but before shipment of the first commercial batches. Nevertheless, certain data must be included in the application to demonstrate that the sterilization or aseptic fill process has been qualified. The inspection team is expected to audit the data to determine their authenticity, accuracy and completeness.

Investigational products are often produced in facilities other than those used for full-scale production (4). These facilities and the associated manufacturing and control procedures are not routinely inspected unless validation of the transfer of the methods from the “investigational” facilities to the full-scale facilities is lacking or questionable. The facilities may be periodically inspected when this is required by national legislation/regulation.

All suppliers and manufacturers of starting materials used in the formulation of pre-approval batches should be identified. The physical characteristics and specifications of the drug substance should be reviewed. This is particularly important for solid oral dosage forms where the physical characteristics of the drug substance often affect uniformity, dissolution and absorption of the dose.

When a pharmaceutical manufacturer replaces the supplier or manufacturer of the drug substance used for the manufacture of the pre-approval batches by another supplier or manufacturer, the application should include data demonstrating that the dosage forms formulated with the drug substance from the two different sources are equivalent in terms of conformity with established specifications, including those given in the application. Specifications should also cover the physical characteristics of the drug substances.

¹ For details of recommended validation programmes, see reference 3.

The addition of any new drug substance and/or dosage form to a production environment must be carefully evaluated in terms of its impact on other products already under production. Any changes that may be necessary in the building and facility must be assessed for their effect on overall compliance with GMP requirements. For example, a new toxic, potent or highly sensitizing product may require additional measures against cross-contamination, and facilities already operating at full capacity may not have adequate space for additional products. The evaluation should also include an assessment of whether any change in the manufacturing authorization is necessary.

Laboratory equipment and procedures must be qualified and validated. Every pre-approval inspection should include an evaluation of laboratory controls and procedures, and a review of some of the raw data used to generate results. The authenticity and accuracy of the data used in the development of a test method should be reviewed.

The inspection team should pay special attention to any newly established facilities, newly installed equipment and/or new raw material suppliers. If unapproved facilities are in use, this should be reported immediately. Inspections of these facilities are not normally required.

7. Sample collection and testing

The pre-approval inspection may include the collection of samples for validation of the analytical methods. Normally the sample size should be sufficient for three full analyses. Unless otherwise indicated by the laboratory, samples of the following sizes may be taken, depending on the dosage form of the product:

- tablets and capsules: 300 units of production;
- injections (single component): 100 units of production;
- injections (combination): 100 units of production plus 10 samples of each component;
- oral powders for reconstitution: 10 units of production;
- oral liquids: 1 litre.

It is important to collect, with the samples, the relevant manufacturer's analytical documentation, namely a copy of the analytical methods used by the inspected laboratory and the report of the analyses performed by the applicant on the batch sampled. A method validation report may be of some use in better understanding and reproducing the analytical methods. Problems encountered in the performance of the analyses may be resolved by an exchange of information between the applicant and the government laboratory.

Samples are tested in accordance with methods described in the application. If there are problems with the methods that require additional information from

the applicant, the laboratory director must review the situation and decide whether the applicant should be contacted. The written request should be included in the documentation submitted to the review analyst.

Each method validation/verification report should contain the following:

- The identification of the test samples received, a description of the product tested, and confirmation of conformity with the product described in the application.
- The original analytical worksheets with calculations, the results of all tests performed, comments by the analyst(s), associated spectra, chromatograms, etc., and a comparison of the results obtained with the applicant's data and with the applicable specifications.
- An evaluation of each test performed by the applicant and the laboratory.
- A recommendation as to whether the methods are acceptable, acceptable only after specified changes have been made, or unacceptable.

If samples have not been collected in the course of a pre-approval inspection, the results of the analytical examination of the samples submitted by the applicant may nevertheless be used as supporting information.

The reserve samples, associated documentation and copies of laboratory reports should be stored in an orderly and retrievable way for a time period specified by national regulations. It is usually recommended that all material should be kept for a minimum of 3 years or for 1 year after the expiry date of the finished product.

8. Follow-up regulatory/administrative decisions

The inspectorate (inspection group of the drug regulatory authority) should recommend withholding approval when significant deviations from GMP requirements and other application commitments have occurred having an adverse effect on the product covered by the application. Examples of significant problems are:

- Misrepresentation of data or conditions relating to pre-approval batches.
- Pre-approval batches not manufactured in accordance with GMP.
- Inconsistencies and/or discrepancies raising significant questions concerning the validity of the records.

If applications are refused because of significant non-compliance with GMP, action must be taken to ensure that the necessary corrective measures are taken.

The drug regulatory authority is expected to advise the applicant that the inspectorate has recommended withholding approval of the application and give the reasons for this recommendation.

References

1. Provisional guidelines on the inspection of pharmaceutical manufacturers. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report*. Geneva, World Health Organization, 1992, Annex 2 (WHO Technical Report Series, No. 823; https://iris.who.int/bitstream/handle/10665/39645/WHO_TRS_823.pdf?sequence=1&isAllowed=y).
2. *Quality assurance of pharmaceuticals. A compendium of guidelines and related materials. Vol. 2. Good manufacturing practices and inspection*. Geneva, World Health Organization, 1999.
3. Good manufacturing practices: guidelines on the validation of manufacturing processes. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 6 (WHO Technical Report Series, No. 863; https://iris.who.int/bitstream/handle/10665/41849/WHO_TRS_863_%28p1-p98%29.pdf?sequence=1&isAllowed=y).
4. Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report*. Geneva, World Health Organization, 1996, Annex 7 (WHO Technical Report Series, No. 863; https://iris.who.int/bitstream/handle/10665/41849/WHO_TRS_863_%28p1-p98%29.pdf?sequence=1&isAllowed=y).

6.5 Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions

Annex 9, WHO Technical Report Series, 1010,
2018

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Background

In recent years both formal and informal collaboration among national regulatory authorities (NRAs) has significantly improved. This, in turn, has strengthened medicines regulatory systems, thereby improving the availability of good quality, safe and effective medical products for patients. A number of regional and supraregional groupings of NRAs are developing, which will facilitate collaboration.

During a World Health Organization (WHO) training symposium on the subject of collaborative registration procedures for national medicines regulatory authorities held in Kenya in September 2016, delegates recommended that the gap in common guidance on best practice for performing desk assessment should be filled. It was proposed that WHO, in collaboration with regulators from Member States, develop guidance that NRAs might leverage in their national regulatory practice and decision-making.

Up to now, there has been no general guidance on approaches and best practices for desk assessment. Desk assessments are conducted in order to verify and confirm compliance with good manufacturing practices (GMP), good laboratory practices (GLP) and good clinical practices (GCP) of foreign facilities for manufacture of finished pharmaceutical products (FPPs) and active pharmaceutical ingredients (APIs), quality control laboratories (QCLs), contract research organizations (CROs) and clinical trial sites.

1. Introduction

NRAs worldwide use systems for the authorization and post-marketing surveillance of medical products that depend upon the assessment of submitted dossiers, variations files and the inspection of FPP and API manufacturers, QCLs and CROs involved in the development, manufacture and distribution of a medical product. Inspections are performed to verify dossier data and to provide evidence that the FPP and API manufacturers, QCLs, CROs and clinical trial sites comply with the relevant good practice (GxP) guidelines and requirements. Thereafter, routine inspections may be conducted depending on the risk rating of the facility.

The performance of on-site inspection of manufacturing, testing and clinical trials as well as the supply and distribution chain outside the NRA's domestic territory is a resource-intensive activity and one that often lies on the critical path to regulatory decision-making. Furthermore, the hosting of multiple regulatory inspections and audits is also a significant overhead for the sites inspected, which adds to the cost of producing the products. Even the best-resourced NRAs face certain limitations and therefore it is regulatory best practice to use quality risk management when prioritizing inspection activities. To make the best use of the limited inspection resources and minimize the need for repeated inspections, it is good practice for national authorities to leverage available and reliable evidence of compliance and noncompliance with good practice

requirements as part of their risk-based inspection planning process, such that there is no on-site inspection without good cause.

Verification and confirmation of compliance with GMP by a manufacturer of an FPP or API in a foreign country may be based on the assessment of evidence that includes the report of a recent inspection of the manufacturer by a competent regulatory authority or another internationally recognized organization.

One element of this risk-based approach is the desk assessment of inspection information from reliable and trusted sources by national or regional authorities in order to decide whether to perform a further inspection before reaching a final decision on marketing authorization, renewal of marketing authorization or another regulatory action. Whereas a desk assessment for GMP and GCP verification and confirmation has been a method used by some organizations and agencies like the WHO Prequalification Team (1), European Member States Agencies (coordinated by the European Medicines Agency (EMA) for centralized marketing authorizations) (2) and the Australian Therapeutic Goods Administration (TGA) (3) for some years, for others it is emerging as an option to be considered.

Such agencies have relied on regulatory decisions made by other agencies, based on bilateral or multilateral agreements depending on the decisions made independently by each individual authority. While not a prerequisite, a range of international and regional formal agreements may be utilized to facilitate the effective management of regulatory decisions in order to increase access to good quality, safe and effective products on the market. These include mutual recognition agreements (MRAs), cooperation agreements (CAs) and memoranda of understanding (MoUs).

Mutual recognition works well if there are common technical standards (including documentation), good regulatory practices; clear procedural legislation in the form of agreement-tracking tools to support the process, trust and political will, with no interference in technical decisions. On the other hand, CAs or MoUs are an option where there is minimal legal obligation. It is also possible to perform desk assessments without a formal agreement.

A desk assessment may be used by an NRA to assess compliance with GMP, GLP and GCP by facilities that manufacture FPPs and APIs. It can also be used to assess CROs, clinical trial sites and outsourced QCLs, where there is an established MRA, CA or MoU, or recognition of a decision made by a competent regulatory authority; Pharmaceutical Inspection Co-operation Scheme (PIC/S) member; or through a WHO prequalification process.

The procedure for the desk assessment will depend on whether the facility was previously inspected by a competent regulatory authority, PIC/S member or under the WHO prequalification scheme, or if an MRA, CA or MoU exists.

The desk assessment process involves submission of documentary evidence by the applicant, usually a manufacturer or representative, to the NRA to demonstrate the conformity of all sites involved in FPP or API manufacturing, or of an outsourced

QCL, CRO or clinical trial site to GMP (the reference is added in the relevant citation), GLP or GCP, respectively. The evidence provided is assessed to determine the level of compliance based on the accepted standards and the scope of the application. The outcome of the assessment process is used as the basis for a regulatory decision that serves as a prerequisite for granting the marketing authorization for a medical product.

Acceptance of data from clinical trial(s) to support a marketing authorization application will rely upon conformance with GCP, including review and approval by an institutional ethics committee where the study was conducted and on obtaining and documenting informed consent of the study subjects if applicable (4).

The option to undertake a desk assessment does not preclude an on-site inspection if the outcome of the assessment does not confirm compliance with the stipulated practices. The confirmation may be granted for a specified period and the process may be subject to recovery of costs. It is important to determine the number of times a desk assessment may be performed before it becomes necessary to conduct a physical inspection, taking into consideration the outcome of the desk assessment, i.e. the number, nature and impact of observations and the integrity of the data provided.

2. Aim and objectives of the guidance

This guidance aims at providing an approach for use by NRAs for assessing compliance with GMP, GLP or GCP using documentation issued by other NRAs in lieu of conducting an inspection of a specific site.

The use of the desk assessment as described in this guidance is intended to provide a way to reduce the necessity for duplication and the frequency of inspections while relying on authentic and reliable documentary evidence from other regulatory authorities. Desk assessment should also reduce the inspection resources needed by both the manufacturing site and the NRAs and result in broader availability of high-quality medicinal products to patients globally. It may also be used by NRAs for continuous evidence-based regulatory decisions and follow-up on quality assurance issues that go beyond marketing authorization.

The guidance also lists the key documents to be submitted by other regulatory authorities and/or manufacturers that provide reliable information about the status of compliance with good practices in manufacturing, quality control and clinical trials of a specified medical product. The essential information and documents that need to be available to conduct the desk assessment in relation to the most relevant GxPs, in this context GMP, GLP and GCP, are described.

The objective of this guidance is to:

- ensure that a standardized procedure is followed for desk assessment of inspection documentation and reports issued by trusted, competent regulatory authorities and of records of corrective actions from inspected sites;

- facilitate a convergent approach and model for exchange and use of inspection information in national and regional decision-making concerning the necessity to perform preapproval and surveillance inspections.

3. Scope of the guidance

This guidance applies to all FPP and API manufacturers (including biologicals and vaccines manufacturers, all sites where APIs are being imported, repackaged or relabelled, and investigational medical product manufacturers), outsourced QCLs, CROs and clinical trial sites that are subjected to GxP inspections in foreign countries. However, the NRA may use desk assessments to set up risk-based inspection plans without loss of regulatory oversight through physical inspections.

The guidance has general geographical applicability for regulatory authorities and United Nations agencies in order to support ongoing harmonization initiatives and optimum use of limited resources. It covers the information and evidence required to undertake a desk assessment process, but not the procedure for on-site inspection, except the process of tracking and review of completion of corrective and preventive action (CAPA). On-site inspection is covered in a separate WHO guidance document (5, 6).

Desk assessment procedures can be used for preapproval, renewal and surveillance inspections. Caution is needed when assessing sites that have failed to meet the specified standard after GxP inspections. However, desk assessments may be appropriate for a site that has failed an inspection, in order to confirm the failure and thus avoid the need for a physical inspection. The NRA takes the ultimate decision on whether it is appropriate to perform a desk review or whether an on-site inspection would be needed.

4. Glossary

The definitions given below apply to the terms used in this guidance. They may have different meanings in other contexts.

active pharmaceutical ingredient. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

agent or local technical representative. Every applicant who is not resident in the country of the national regulatory authority (NRA) should appoint a person in that country to be an agent (local technical representative). The appointment should be notified to the NRA by submitting a letter of appointment supported by powers of

attorney duly notarized in the country of origin, and registered with the registrar of companies in the country of the NRA.

applicant. A person who applies for marketing authorization of a medical product to the national regulatory authority, who must be the owner of the product. The applicant may be a manufacturer or the party applying for a product certificate. After the product is registered, the applicant becomes the marketing authorization holder.

bioequivalence. Two medical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailability, in terms of rate (C_{\max} and t_{\max}) and extent of absorption (area under the curve), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

clinical trial (or clinical study). Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamics effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

competent regulatory authority. Any organization that has a legal authority or power to perform a designated regulatory function for authorization of a medical product: the national regulatory authority in the Member State.

cooperation agreement. A formal business document outlining the basic terms of an agreement with another individual, group or entity. It is one of the first steps towards a more detailed contract. Alternative names include, but are not limited to, memorandum of understanding, cooperation contract or collaboration agreement.

desk assessment. The evaluation of documentary evidence by a competent regulatory authority recognized by the national regulatory authority, for compliance with the required good practices (good manufacturing practices (GMP), good laboratory practices and good clinical practices) in support of marketing authorization and other regulatory decisions. Desk assessment may be performed in support of a new marketing authorization, or for routine GMP inspection (including in the frame of specified product(s) life-cycle management as required).

finished pharmaceutical product. A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

good clinical practices. In this context the term means a standard for design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials in a way that provides assurance that the data and reported results are credible, accurate and that the rights, safety and well-being of trial subjects are protected.

good laboratory practices. A quality system concerned with the organizational process and the conditions under which nonclinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

good manufacturing practices (GMP). That part of quality management which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial authorization or product specification. GMP are concerned with both production and quality control. GMP are aimed primarily at managing and minimizing the risks inherent in pharmaceutical manufacture to ensure the quality, safety and efficacy of products.

information sharing. An exchange of data between individuals or entities outside the traditional organizational boundaries, to achieve a common goal in terms of better policies and to deliver better services. This may mean that one party is disclosing information while the other is collecting the information or both parties are mutually disclosing and collecting information.

manufacture. All operations of purchase of materials and products, production, quality control, release, storage, distribution of medical products and the related controls.

manufacturer. A manufacturer is a natural or legal person who holds a manufacturing authorization and has responsibility for manufacturing of a medical product or active pharmaceutical ingredient.

marketing authorization (product licence, registration certificate). A legal document issued by the competent regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself and includes details of packaging, labelling and shelf life.

medical product. A term that includes medicines, vaccines, diagnostics and medical devices.

memorandum of understanding (MoU). A formal agreement between two or more parties. Companies and organizations can use MoUs to establish official partnerships. MoUs are not legally binding but they carry a degree of seriousness and mutual respect, stronger than a gentlemen's agreement.

mutual recognition agreement. This is defined as the reciprocal adoption or acceptance of regulatory decisions or outcomes in other partner states in form of a legal agreement. It is stronger than a gentlemen's agreement and is usually binding.

Pharmaceutical Inspection Co-operation Scheme (PIC/S). This is a non-binding, informal cooperative arrangement between regulatory authorities in the field of good manufacturing practices of medical products for human or veterinary use.

pharmaceutical product. Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings.

quality control. All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics

quality management system. An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

quality system. The sum of all features that are necessary to implement an organization's quality policy and meet quality objectives. It includes organizational structure, responsibilities, procedures, systems, processes and resources. Typically these features will be addressed in different kinds of documents, such as the quality manual and documented procedures.

5. Essential elements of desk assessment

5.1 High-level support and cooperation

Interagency communication can facilitate greater regulatory convergence. This in turn can increase the efficiency and quality of medical product development and the NRA review processes as well as improving patients' access to quality medical products. This not only entails accessing information from the public websites of other NRAs, such as guidelines, decisions and product recalls, but also actively sharing information between NRAs, in particular with respect to inspection findings during application review and for decision-making.

The legal framework and governance structure of the NRA should include provisions on support and collaboration with other agencies in making regulatory decisions. Legal provisions (laws and regulations) that allow reliance on foreign NRA inspections and enforcement actions based on well-defined criteria should be established and implemented. Such recognition can take the form of MRAs, CAs or MoUs between collaborating inspectorates and could entail agreements that would enable bilateral or multilateral commitment and exchange of information on specified sites.

MRAs are usually binding and may require inspectorates at the same level of development with the appropriate organization and funding to fulfil the responsibility of protecting and promoting public health. Where such recognition exists, fewer requirements are needed to determine compliance with GMP, GLP and GCP of foreign manufacturing sites, CROs and outsourced QCLs, given the level of cooperation and trust established.

5.2 Commonality of quality management systems in inspectorates

There should be a quality system in place based on recognized international standards, namely the WHO quality management system (QMS) or International Organization for Standardization (ISO) QMS standards. The QMS should be established, implemented and maintained throughout the period of recognition or reliance. The primary purpose of a QMS is to ensure that adequate quality standards are maintained.

Adopting common standards for quality system requirements (within GMP, GLP or GCP of the NRA) helps to achieve consistency in inspection standards between inspectorates and thus facilitates mutual recognition and reliance.

5.3 Convergent standards of good practices

WHO has published standard requirements for compliance with GMP (7) and other good practices including *Good practices for pharmaceutical quality control laboratories* (8) and GCP (4, 9). These serve as a measure of the standards established by the manufacturers in order to deliver and supply a good quality and safe product. The NRA should have similar standards of GxP in order to facilitate uniform desk assessment.

5.4 Reliability and accuracy of information

Applicants are responsible for ensuring that information provided for desk assessment is reliable and not false or misleading.

Mechanisms and controls should be established to ensure that the information provided by the applicant is authentic, legible, current and accurate. There should be strong confidence that the information provided relates to the same strength and specifications of the product and to the same site, workshop or production line (use of unique facility identifiers should be considered); and should accurately relate to the product under assessment, without any false information.

Controls should be established and documented by the NRA to ensure that the information provided by the applicant is secured and remains confidential.

5.5 Management tools to support consistent and objective assessment

Well-structured and up-to-date assessment tools and procedures should be adopted to enable uniform and consistently objective assessment of the documents provided. Personnel involved in the assessment process should have an acceptable level of training and experience with GMP, GLP or GCP. They should also be trained to use the assessment tools and procedures consistently without bias, and to be able to detect inconsistent and inaccurate information regarding the product under assessment. Validated electronic assessment tools (software applications) may be used to perform the desk assessments. Although paper-based systems may also be used, electronic tools are preferred.

5.6 Risk-based assessment of available information

Even the best-resourced NRAs are subject to limitations in terms of time, funding and personnel, and therefore it is regulatory best practice to apply quality risk management as defined and outlined in ICH Q9: Quality risk management, in prioritizing inspection activities (10, 11). The aim of the desk assessment process should be to provide to the

NRA, in a timely manner, the required assurance that the site in question demonstrates an acceptable level of GxP for the FPP, API or trial under assessment.

The assessment should take into consideration and focus on the critical products and critical processes in the manufacture of a specified product in relation to patient risk, based on the knowledge that other competent and trusted inspectorates have inspected and approved the site of manufacture.

Key factors to consider include the origin of the information and its authenticity, the location of the site of manufacture, complexity and type of the product (whether sterile or biological) and the risk to the patient (12).

5.7 Mutual trust and confidence among inspectorates

Joint inspections may be conducted by countries within the same region or countries that are party to a relevant agreement. Through such interactions, regulators may be able to build confidence, share information and experiences in order to be able to rely on others' inspection outcomes and regulatory decisions. Joint inspections also serve as a basis for desk assessments through building mutual trust and identifying barriers to reliance on other regulators' inspection outcomes and devising solutions to overcome them. Building mutual trust and confidence involves exchange of information, identifying areas of collaboration, work sharing and eventually binding through a legal agreement between collaborating NRAs.

Some competent NRAs are already using these models successfully. Examples include the United States of America (USA) Food and Drug Administration's MRA with the European Union, Health Canada's MRA with the European Union, and the TGA's risk-based desktop assessment process. The TGA's process comprises MRA and compliance verification pathways, which are essentially desk reviews. Those two pathways can result in cost savings for both the manufacturer, who does not have to bear the cost of hosting another inspection, and the regulator, who saves on personnel time and other resources.

5.8 Quality assurance of the desk assessment process

Quality assurance of the desk assessment process involves inspiring confidence that the requirements of the assessment process will be fulfilled. This would require documented evidence of compliance of the inspectorate function with a QMS¹ over a period of three to five years.

NRAs should create a cycle for the process of reviewing desk assessments, including timelines for applicants' responses.

¹ For example, ISO/International Electrotechnical Commission (IEC) 17020 *Conformity assessment – requirements for the operation of various types of bodies performing inspection*, PIC/S *Quality management system for inspectorates* or ICH Q9 *Quality risk management*.

5.9 Communication of assessment outcomes

Communication of the outcome of the desk assessment process should be transparent and timely. Communication should focus on the quality of the product and the regulatory decisions between the authorities in the importing country and exporting country, the manufacturers and any other relevant third party, such as procurement agencies. The outcome of the desk assessment should be communicated to the applicant whether the result is an approval, a deferment or a rejection of an application for GxP assessment, and to the responsible NRA.

If a rejection leads to a regulatory decision to conduct an on-site inspection, a statement of the reasons should be provided, with details of the documents, information and regulatory requirements taken into account in reaching the decision. An appeal mechanism, including a time frame within which applicants may lodge an appeal, should also be in place. The NRA should reserve the right to conduct an inspection of any site.

6. Sources of good information and related challenges

Trusted sources of information are available either in the public domain or from the NRAs. The amount of detail provided in the information may vary depending on applicable restrictions and rights of the owners. Websites of NRAs may provide information on non-compliant facilities, market complaints and product recalls, among others.

Certificates, reports or other documents issued by competent regulatory authorities also provide information about a specified manufacturer, outsourced QCL, CRO or clinical trial site.

6.1 Official websites with databases

NRAs and organizations such as WHO and EMA have websites where information on facilities' compliance and noncompliance with GxP is available. Some websites provide GMP certificates and inspection reports together with other information about medicines, pharmaceutical manufacturing facilities, QCLs and clinical trials. Information may also be obtained on medicine sampling and results of the testing, including samples that failed analysis, product recalls and rapid alerts. The website consulted should be current and regularly updated. Certificates presented by applicants for marketing authorization should be verified using the information available on the websites of NRAs or by contacting the relevant NRA directly. The NRA is responsible for checking that information is current and complete.

6.2 Authenticity of documents

It is important that documentary evidence provided by the applicant as the basis for granting approval for GMP, GLP or GCP be current, accurate and authentic. It is the

responsibility of the applicant to ensure this. The applicant should include a cover letter with the application stating that all the documents submitted are authentic and correct. NRAs may request that information such as inspection reports and certificates granted by NRAs be notarized or certified.

Submission of inaccurate or false information may result in declaration of the manufacturer, QCL or CRO as noncompliant.

6.3 Failure to submit documentary evidence

If the applicant is unable to provide adequate documentary evidence, including information on current compliance, or to submit the documents before a specified deadline, or fails to submit documents as required, the application for desk assessment may be rejected, leading to a decision to conduct an on-site inspection. In such circumstances, approval of GMP, GLP or GCP should only be granted after the on-site inspection has been conducted, and the manufacturer, CRO, clinical trial site or outsourced QCL has been found compliant.

7. Submission and assessment of documentary evidence and information

7.1 Submission of application for desk assessment and documentary evidence

Prior to assessment, an application for desk assessment for each site should be submitted by the applicant to the NRA. Applications may be required for preapproval, renewals and surveillance inspections, as specified by the NRAs in the respective inspection guidelines and procedures.

7.2 Assessment of documentary evidence and information

Desk assessment involves a detailed evaluation of the specified documentary evidence supplied by the applicant. It will include an assessment of reports of recent inspections of the relevant manufacturing site undertaken by a competent regulatory authority, together with other available regulatory information. Desk assessment for compliance of facilities manufacturing FPPs and APIs with GMP, GLP or GCP can be used where the NRA has an agreement or understanding on exchange of information, such as an MRA, CA or MoU.

In accordance with international agreements with certain countries, the NRA may accept compliance of a foreign site with GMP, GLP or GCP requirements based on a current certificate or approval letter issued by the regulatory agency of the other party to the MRA.

Marketing authorization may be granted by the NRA on the basis of a current certificate or approval letter issued within the scope of an MRA. The scope of the

manufacturing activities indicated in the application should be within the scope of the activities covered by the certificate or approval letter.

Generally, where an MRA has been established:

- a. a copy of the manufacturing authorization granted by national authorities together with a certified translation, where this is not in English, may suffice.

Where a CA or other bilateral or multilateral arrangement has been established, the document specified in a. above should be provided in addition to the following essential documents:

- b. a site master file (*13*) whose approval date was not more than one year ago, and any forecast modifications, together with legible colour printouts of water treatment and air-handling systems, including pipeline and instrumentation drawings in A3 or A2 format;
- c. a list of all the products and dosage forms manufactured on-site. The list should include proprietary names and International Nonproprietary Names (INN);
- d. a copy of the last inspection report issued by the NRA with a certified translated copy where this is not in English, and GMP, GLP or GCP certificates or an approval letter with a certified translated copy where this is not in English (production-line specific);
- e. current full inspection report(s) for inspections performed by a competent regulatory authority in the past three to five years, with a certified translated copy where this is not in English;
- f. proof of CAPA implementation and final decision by the NRA related to observations or deficiencies noted in the latest inspection report or any warning letter or equivalent regulatory action (production-line specific);
- g. the most recent product quality review(s) (PQR)(s) of the concerned product(s); PQR(s) (*4*) or equivalent documentation covering all required subsections and trend results should be presented; proprietary information for vaccines is not required;
- h. the completed batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant product(s);
- i. a list of any recalls in the past three years related to products with quality defects.

The following documents may be evaluated while performing desk assessments:

- a confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the product(s) has been performed and all matters dealt with;

- master batch manufacturing and packaging record(s) of the product(s) of interest;
- a copy of any warning letter, or equivalent regulatory action, issued by any authority to which the site provides or has applied to provide the product;
- out-of-stock situations.

The evidence lists required for desk assessment of compliance with GMP, GLP or GCP for each type of facility and collaborative arrangement are listed in Table A9.1 and the specific documentary evidence required is presented in Table A9.2.

Table A9.1

Type of facility and evidence documents required for desk assessment^a

Type of facility	Where an MRA exists	Where a CA or MoU exists; or member of PIC/S; or competent NRA regulator; or WHO prequalification scheme	Where no MRA, CA or MoU exists; or non-member of PIC/S; or WHO prequalification scheme
Nonsterile products facilities • FPP • API	Evidence list A	Evidence list B	On-site GMP inspection
Sterile products facilities • FPP • API	Evidence list A and certification to relevant ISO standards for sterilization facility ^b	Evidence lists B and C	On-site GMP inspection
Outsourced (contract) testing laboratory; and outsourced sterilization	Evidence list A	Evidence list D	On-site laboratory inspection On-site GMP inspection

Table A9.1 *continued*

Type of facility	Where an MRA exists	Where a CA or MoU exists; or member of PIC/S; or competent NRA regulator; or WHO prequalification scheme	Where no MRA, CA or MoU exists; or non-member of PIC/S; or WHO prequalification scheme
CRO or clinical trial site <ul style="list-style-type: none">• clinical facility• clinical laboratory• bioanalytical laboratory• company performing pharmacokinetics statistical analysis	Evidence list E	Evidence lists E and F	On-site GLP or GCP inspection

API: active pharmaceutical ingredient; CA: cooperation agreement; CRO: contract research organization; FPP: finished pharmaceutical product; GCP: good clinical practices; GLP: good laboratory practices; GMP: good manufacturing practices; ISO: International Organization for Standardization; MoU: memorandum of understanding; MRA: mutual recognition agreement; NRA: national regulatory authority; PIC/S: Pharmaceutical Inspection Co-operation Scheme.

^a Explanations of the evidence lists are provided in Table A9.2.

^b If applicable to the manufacturing facility or activity.

A list of the documents that should be provided for desk assessment is given in Table A9.2. The documents required for desk assessment of manufacturing sites are indicated in evidence lists A, B, C and D; for outsourced QCL, they are indicated in evidence lists A and D and for CROs and clinical trial sites, they are indicated in evidence lists E and F.

Table A9.2
Documentary evidence requirements for desk assessment

	Required evidence	Comments and exceptions
Evidence list A	Current GMP certificate or approval letter GLP or ISO/IEC 17025 certification for outsourced laboratory	Certificates must be sufficient to cover the scope of the GMP compliance application

Table A9.2 *continued*

	Required evidence	Comments and exceptions
Evidence list B	Current GMP certificate or approval letter	GMP agreements may be requested if the foreign manufacturer performs the release for supply function
	Current manufacturing licence	The manufacturing licence should show the scope of products and activities approved by the NRA
	Regulatory inspections conducted within the past three years and a copy of the most recent inspection report issued by the competent regulatory authorities as stated in Table A9.1	A list of all inspection reports applicable to the scope of the application is required. These may be sent to the NRA directly from the manufacturer CAPA evaluation for the recent inspection report should be provided
	Market complaints register	For the previous three years, including one investigation report for one of the complaints classified as high risk to public health The complaint register should be applicable to the products named in the application
	Details of any regulatory actions in the past three years	For example, product alerts, warning letters, import alerts, recalls due to defects
	Site master file, quality manual or equivalent	Site master file ^a Site master file is not required if the scope of the application is only for the step of release for supply
	List of products intended for supply in the recipient country	

Table A9.2 *continued*

	Required evidence	Comments and exceptions
	<ul style="list-style-type: none"> • PQR report; • process validation report; and • batch records (batch manufacturing, packaging and testing) for each product for which marketing authorization is being applied 	<p>The PQR reports should be provided for each product. If there are multiple products, one PQR report is required for each FPP dosage form for which an application is being made</p> <p>The batch records of a product for each FPP dosage form manufactured in the past 6 to 12 months; and the corresponding process validation reports and annual product quality review reports</p>
	List of reprocessed or reworked product batches in last year (or last two years)	
Evidence list C	Validation master plan	Not required if the scope of the application is only for the step of release for supply
	Aseptic processing and filling validation reports if applicable	Required if the application concerns products that are not terminally sterilized
Evidence list D	Current GMP certificate, or ISO/IEC accreditation certificate or WHO prequalification	For outsourced testing laboratories, a GLP certificate issued by a recognized regulatory authority or a current ISO/IEC 17025 accreditation certificate or prequalification of the laboratory by WHO is required
		For outsourced sterilization facilities, certification to applicable ISO sterilization standards (e.g. ISO 11137, ISO 11135) is necessary
	Quality manual, laboratory manual or equivalent	The quality manual or laboratory manual should be written in accordance with the principles of <i>WHO good practices for pharmaceutical quality control laboratories</i> (8), or as per the ISO/IEC 17025 <i>General requirements for the competence of testing and calibration laboratories</i> (14).

Table A9.2 *continued*

	Required evidence	Comments and exceptions
	Contract or agreement between the FPP or API manufacturer and the outsourced testing laboratory or sterilization institution	A copy of the contract or agreement clearly describing the roles and responsibilities of the manufacturer and the testing laboratory or sterilization institution should be submitted
	A list of tests a laboratory is authorized to perform as per the scope of its accreditation according to the ISO/IEC 17025 or WHO prequalification	The scope of activities of the outsourced laboratory should include the type, range and volume of testing and/or calibration, validation and verification activities it undertakes
	For botanical ingredients, evidence that authenticated standard reference materials are used	
	Out-of-specifications (OOS) procedure	Records of three OOS including at least one assigned to a laboratory error
Evidence list E	Current GCP or GLP certificate or approval letter	GCP/GLP certificate or approval letter issued by the NRA; non-use of disbarred investigators or firms
Evidence list F	Clinical trial approval by the NRA	Provide a list summarizing the approved trials and their outcome Provide complete study report if no application has been submitted for marketing authorization of a product Where applicable, reports from a data safety monitoring board or independent safety monitors should be provided
	Copy of IRB/IEC clinical trial approval	Provide approved protocol, amended protocol and consent form Provide a list of committee members of the IRB/IEC

Table A9.2 *continued*

Required evidence	Comments and exceptions
Clinical trial master file	<p>Responsibilities of the sponsor and clinical investigator should be reported</p> <p>Records of management and assessment of subcontracted vendors should be provided</p> <p>Deviation management and procedures for handling the investigational product should be made available</p>
Inspections conducted within the past three years and a copy of the most recent inspection report issued by the competent regulatory authority as stated in Table A9.1	<p>A list of all inspection reports applicable to the scope of the application is required. These may be sent to the NRA directly from the manufacturer or CRO</p> <p>Provide the following reports:</p> <ul style="list-style-type: none"> • reports by the NRA; • clinical monitoring reports by the sponsor or the CRO (if monitoring tasks were outsourced to a CRO)
Concerns or alerts raised by the NRA and any other responsible authority	Provide details of investigation of any instances of noncompliance and how they were addressed

API: active pharmaceutical ingredient; CAPA: corrective and preventive action; CRO: contract research organization; FPP: finished pharmaceutical product; GLP: good laboratory practices; GMP: good manufacturing practices; IEC: independent ethics committee; IRB: institutional review board; ISO: International Organization for Standardization; NRA: national regulatory authority; PQR: product quality review.

^a Refer to WHO Technical Report Series, No. 961, Annex 14, for guidelines on compiling a site master file (13).

7.3 General requirements for documents

Documents to be submitted to NRAs as evidence of compliance should adhere to the following general requirements.

- All certificates and other supporting documents should be in English or in a nationally accepted language.
- Where the document is not in English or a nationally accepted language, it should be submitted with a certified translation.
- Translated documents must be accompanied by a signed and dated statement by the certified translator, stating that each is a true and accurate translation of the original document.

- Submitted documents should be the most recent and reflect current activities and practices, and dated (expired or superseded documentation cannot be used).
- Documents must provide sufficient information to cover the scope of activities for which confirmation of GxP compliance is sought.

All documents, whether the original format is paper or electronic, are to be submitted electronically (for example as DVDs CDs, etc.) and are not required to be certified as original copies unless requested by the NRA. Certification of a document may be requested if, for example, there is concern over the validity of the supplied documents. The NRA can request certified copies of original documents at any time. Certified copies must be legible and authenticated as true copies by either:

- an official of the regulatory agency of a country that is a party to an MRA, or a partner to an MoU or a CA, WHO prequalification, stringent regulatory authority, regulator; or
- a public notary (who must include details of the relevant practice certificate or licence number).

Figure A9.1

Model declaration form for the front page of a certified document

Declaration of authenticity

I, the undersigned, as a _____ for the state of _____, country _____ declare that the attached copy of the document issued by _____ and certified by me, is a true and accurate copy of an original document presented to me for certification.

_____ Date: _____ / _____ / _____

Full names [signature] day/month/year

8. Regulatory actions and reporting of serious instances of noncompliance

Regulatory actions should be taken by NRAs in response to the reporting of serious instances of noncompliance, such as a variation from the registered product that has a direct impact on the safety of a patient or subject, and follow applicable procedures for appropriate investigations.

The impact of the noncompliance should be assessed by the NRA to ascertain the potential risk to public health, supply and availability of affected medicines. This

assessment should take into consideration the risk of exposure to national shortages having undesirable safety and financial implications.

The following are some of the actions that can be taken by the NRA in response to confirmed reports of serious noncompliance:

- issuance of a rapid public alert to collaborating partners;
- issuance of a noncompliance letter;
- suspension, revocation, withdrawal or cancellation of GMP, GLP or GCP certificate;
- suspension of certificate of suitability;
- institution of a recall;
- suspension of supply or importation;
- prosecution.

8.1 Communication and information exchange

There should be a mechanism for exchange of information among inspectorates, for example, a shared web-based portal for communication of serious instances of noncompliance in a timely and secure manner. The NRA should have a process for information exchange and use of identifiers for tracking enquiries and applicants' responses.

If facilities are found to have serious issues of noncompliance with GMP, GLP or GCP guidelines, this should be communicated to stakeholders and partners. The regulatory decision and action taken should be explained to the stakeholders, including the analysis of the risk and threats to the patient.

9. Responsibilities of the applicant

The main responsibilities of an applicant for GMP, GLP or GCP desk assessment are summarized below.

- Ensuring that all required evidence documents are submitted with applications for GMP, GLP or GCP desk assessment. Incomplete applications may be rejected.
- Remitting all application fees at the time of lodging an application for GMP, GLP or GCP desk assessment.
- Submitting applications for renewal of a GMP, GLP or GCP certificate prior to the expiry of the current certificate, according to a deadline specified by the NRA.
- Promptly submitting any additional information that may be requested by the NRA during an assessment. Failure to provide required documents in time may result in the application being rejected.

References and further reading

References

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10. ICH Q9 quality risk management. Geneva: The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (<https://www.ich.org/page/quality-guidelines>).
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12. Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 5 (WHO Technical Report Series, No. 986; https://iris.who.int/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1&isAllowed=y).

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Further reading

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- ISO 11135:2014. Sterilization of healthcare products – ethylene oxide – requirements for the development, validation and routine control of a sterilization process for medical devices. Geneva: International Organization for Standardization; 2014.
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Appendix 1

Model report format for desk assessment for finished pharmaceutical products and active pharmaceutical ingredient manufacturers

Part 1. General information	
a) Particulars of the applicant	Name of applicant, physical address, postal address of applicant (if different from physical address), 24-hour telephone numbers, fax, email address
b) Particulars of the manufacturer	Name of manufacturer, physical address of manufacturer including the block and/or unit number, postal address of manufacturer (if different from physical address), 24-hour telephone number(s), fax, email address, contact person
c) Activities performed on the site	For example, manufacture of APIs, manufacture of FPPs, intermediates or bulk packaging, laboratory testing, batch release, warehousing, primary and secondary packaging
d) Date of last inspection by the NRA	Date when the last inspection was carried out, name of the national medicines regulatory authority that carried out the inspection
e) Production and packaging lines applied for	For FPP: dosage form line, category: beta lactam, non-beta lactam, biologicals, vaccines, hormones, cytotoxic products For API: name of API
f) Authorized representative of marketing authorization holder in the recipient country	For example, representative, agent
Part 2. Documentary evidence (comment on adequacy of information provided)	
a) Current site master file	Comment on date, completeness and adequacy in accordance with WHO or PIC/S guidelines for writing site master file
b) List of all regulatory inspections carried out in the past three years	Name of all the regulatory authorities that carried out the inspection, dates when the inspection was carried out, inspection outcome

Table continued

Part 2. Documentary evidence (comment on adequacy of information provided)	
c) Copy of valid manufacturing licence granted by the NRA together with a certified translation, if not in English	Number of manufacturing licence, name of regulatory authority that granted the licence, validity of the manufacturing licence and scope
d) Copy of valid GMP certificate granted by the national medicines regulatory authority together with a certified translation, if not in English	Number of GMP certificate, name of NRA that granted the certificate, validity of the GMP certificate and scope
e) List of products manufactured at the site and those to be exported to the country of import	List of products, dosage form (where applicable), list of registered products and those to be registered
f) Notarized copy of inspection report(s) from the national medicines regulatory authority and/or that from WHO prequalification (whichever is applicable) carried out within the past three to five years	<ul style="list-style-type: none"> • Name of the regulatory authority that carried out the inspection, dates of the inspection, scope of inspection, findings and recommendations, list of findings of noncompliance, conclusion • CAPA reports submitted and found satisfactory for the most recent inspection (adequacy of CAPA, timelines)
g) Performance of the company's products on the market over the past three years	Any product alerts, warning letters, market complaints, product failure, product recall or any unacceptable findings for the product(s) in scope
h) Reports of product quality review	For products for which marketing authorization is being sought or renewed: assess the consistency of the processes, trends, specifications, process changes, recalls, returns, market complaints, deviations from critical parameters, in-process controls, quality control tests, stability study data (select product of interest)
i) Validation master plan	Validation policy, utilities qualification, equipment qualification, procedures, protocols, reports, cleaning, personnel qualification, process validation, analytical method validation, computer validation, revalidation, requalification, validation matrix
j) Process validation for one of the products marketed or to be registered in the country of import	Comment on adequacy

Table *continued*

Part 2. Documentary evidence (comment on adequacy of information provided)

- | | |
|---|---------------------|
| k) One batch manufacturing record (BMR) for each product together with the master batch record including the packing and analytical part (with a certified translation of the original BMR where applicable); BMR should refer to a product marketed or to be registered in the country of import | Comment on adequacy |
| l) Out-of-specification (OOS) procedure: records of three OOS including at least one assigned to a laboratory error | |
| m) List of reprocessed or reworked product batches in the past two years | |

Part 3. Recommendation

1. Recommended for a GMP compliance approval?
(Provide recommendation based on the results of the assessment done in Parts 1 and 2)

2. If Yes, list production lines, product, pharmaceutical active ingredient recommended:

3. If No, state reasons and the relevant sections of the guideline(s) below:

*Table continued***Part 4. Evaluation team****First assessor**

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)**Second assessor**

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)

API: active pharmaceutical ingredient; CAPA: corrective and preventive action; FPP: finished pharmaceutical product; GMP: good manufacturing practices; NRA: national regulatory authority; PIC/S: Pharmaceutical Inspection Co-operation Scheme.

Appendix 2

Model report format for desk assessment of quality control laboratories

Part 1. General information	
a) Particulars of the applicant	Name of applicant, physical address, postal address of applicant (if different from physical address), 24-hour telephone numbers, email address
b) Particulars of the quality control laboratory (QCL)	Name of QCL, physical address of QCL, postal address of the laboratory (if different from physical address), 24-hour telephone number(s), email address, contact person
c) Date of last inspection by SRA, WHO or accreditation body for ISO/IEC 17025	Name of NRA or accreditation body that carried out the inspection, dates when the inspection was carried out and the inspection outcome
Part 2. Documentary evidence (comment on adequacy of information provided)	
a) Copy of appropriate certificate or approval granted by a recognized regulatory authority or accreditation certificate granted by accreditation body for ISO/IEC 17025 together with a certified translation, if not in English	Number/reference of appropriate certificate or approval or ISO/IEC 17025 certificate, name of regulatory authority that granted the certificate and validity of the certificate
b) Scope of accreditation	Indicate the analytical methods and techniques
c) Current quality manual, laboratory manual or equivalent	Comment on adequacy ^a
d) Contract between the manufacturer and contract laboratory and its subcontractors if applicable (where testing is outsourced)	Comment on adequacy of the agreement stating responsibilities of the parties
e) List of all inspections carried out in the past three years by a regulatory authority or accreditation body	Provide the list of regulatory authority or accreditation body indicating the name, date of inspection and outcome in the inspection

Table continued

Part 2. Documentary evidence (comment on adequacy of information provided)	
f) Copy of inspection report(s) from regulatory authority or accreditation body and/or from WHO prequalification (whichever is applicable) carried out within the past three to five years	Name of the regulatory authority or accreditation body that carried out the inspection, dates of the inspection, scope of inspection, findings and recommendations, list of instances of noncompliance, conclusion
g) CAPA reports submitted and found satisfactory for the most recent inspection	Comment on adequacy
h) Register of OOS, OOS procedure and investigation reports of at least three OOS assigned to laboratory error in past one year handled	Comment on adequacy
Part 3. Recommendation	
1. Recommended for a GMP compliance approval? <i>(Provide recommendation based on the results of the assessment done in Parts 1 and 2)</i>	
2. If Yes, state laboratory testing activities/product analysed:	
3. If No, state reasons and the relevant sections of the guideline(s) below:	

Table continued

Part 4. Evaluation team

First assessor

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)

Second assessor

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)

CAPA: corrective and preventive action; ISO/IEC: International Organization for Standardization/International Electrotechnical Commission; NRA: national regulatory authority; OOS: out of specification; SRA: stringent regulatory authority.

^a Refer to WHO good practice for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957).

Appendix 3

Model report format for desk assessment for contract research organizations and clinical trial sites

Part 1(i). General information – study	
a) Particulars of the applicant	Name of applicant, physical address, postal address of applicant (if different from physical address), 24-hour telephone numbers, email address
b) Particulars of the organization	Name of research organization, physical address, postal address (if different from physical address), 24-hour telephone number(s), fax, email address
c) Title of the study	
d) Particulars of the bioanalytical laboratory	Name of bioanalytical laboratory, physical address of bioanalytical laboratory, postal address of the laboratory (if different from physical address), 24-hour telephone number(s), fax, email address
e) Particulars of the sponsor	Name of sponsor, 24-hour telephone number(s), fax, email address, contact person
Part 1(ii). General information – site quality management system	
a) Date of last inspection by NRA (if applicable)	Dates when the last inspection was carried out; name of the national medicines regulatory authority that carried out the inspection
b) Particulars of the investigator's current curriculum vitae and/or qualifications	

Table continued

Part 2(i). Documentary evidence – study	
a) Copy of institutional review board (IRB)/independent ethics committee clinical trial/bioequivalence (BE) study approval	For multicentre trials, only the study approval issued by the IRB/IEC of the coordinating investigator of the trial is required
b) Copy of clinical trial/BE approval granted by a competent national medicines regulatory authority with a certified translation, if not in English	Name of the approving authority, validity of approval (study)
c) Copy of clinical trial/BE/bioavailability study protocol and any amendments ^b	Comment on the trial design, selection and withdrawal of subjects, treatment of subjects, assessment of efficacy, assessment of safety, statistics, data handling and record-keeping, ethics, financing and insurance, quality control and quality assurance, and publication policy
d) Copy of investigator's brochure	Confidentiality statement, physical chemical and pharmaceutical properties and formulation, nonclinical studies, effects in humans, summary of data and guidance for the investigator
e) Copy of current clinical trial/BE reports including safety reports	Comment on adequacy and compliance with the protocol (study)
f) Copy of clinical trial monitoring report by the sponsor or contract research organization (CRO)	
Part 2 (ii). Documentary evidence – site quality management system	
a) Copy of current GCP/GLP certificate or regulatory approval	
b) Number of clinical trials/BE study approvals granted by a national medicines regulatory authority in the past five years, with a certified translation, if not in English	State number of approved clinical trials/BE studies and their outcomes, name of the approving authority, validity of approval

Table continued

Part 2 (ii). Documentary evidence – site quality management system	
c) Copy of current clinical trial master file ^a (make reference to the quality assurance mechanism for CRO) Documentation on the responsibilities of the sponsor and clinical investigator, management and assessment of subcontracted vendors should be provided.	Comment on adequacy of deviation management and procedures for handling the investigational product
d) List of all inspections carried out in the past three years	Clinical monitoring reports by the sponsor or the CRO (if monitoring tasks were outsourced to a CRO)
e) Copy of inspection report(s) from national medicines regulatory authority and/or that from WHO prequalification (whichever is applicable) carried out within the past three to five years	Including bioanalytical method validation and compliance with GLP
f) Provide evidence of NRA oversight including concerns raised and alerts, if any	
g) Copy of study monitoring report by the sponsor or CRO (where applicable)	
Part 3. Recommendation	
1. Recommended for a GMP compliance approval? <i>(Provide recommendation based on the results of the assessment done in Parts 1 and 2)</i>	
2. If Yes, study/clinical trial site recommended:	
3. If No, state reasons and the relevant sections of the guideline(s) below:	

Table continued

Part 4. Evaluation team

First assessor

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)

Second assessor

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)

GCP: good clinical practices; GLP: good laboratory practices; NRA: national regulatory authority.

a Guidelines for good clinical practice E6 (R1), Current Step 4 Version, 10 June 1996. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (<https://www.ich.org/page/efficacy-guidelines>).

b Guidance for organizations performing in vivo bioequivalence studies (revision). In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 9 (WHO Technical Report Series, No. 996).

6.6 Assessment tool based on the model quality assurance system for procurement agencies: aide-memoire for inspection

Annex 4, WHO Technical Report Series 986,
2014

1. Introduction	1304
2. Purpose	1304
3. Scope	1304
4. Assessment tool	1305

1. Introduction

The Expert Committee on Specifications for Pharmaceutical Preparations of the World Health Organization (WHO) adopted a model quality assurance system for procurement agencies (MQAS) during a meeting in Geneva, Switzerland in 2005. This was subsequently published as Annex 6 in the Technical Report Series, No. 937 in 2006.

The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) Secretariat coordinated this project with the aim of preparing a harmonized assessment tool based on the WHO documents: *Model quality assurance system for procurement agencies (MQAS)*; WHO *guidelines on good storage practices (GSP)* and WHO *guidelines on good distribution practices (GDP)* (for current versions, see www.who.int/medicines).

This harmonized tool was developed by a working group consisting of representatives from the following organizations: Committee for Medicinal Products for Human Use (CHMP), Crown Agents, global drug facility (GDF), Global Fund to Fight AIDS, Tuberculosis and Malaria, International Committee of the Red Cross (ICRC), International Development Association (IDA), Médecins Sans Frontières (MSF), Management Sciences for Health (MSH), Partnership for Supply Chain Management (PFSCM), Quality Medicines for All (QUAMED), United Nations Children's Fund (UNICEF), United Nations Office for Project Services (UNOPS) and United States Agency for International Development (USAID).

2. Purpose

This harmonized tool was developed by the working group with the objective that it could result in better use of resources by coordinating procurement agency (PA) assessments; and working towards mutual recognition of the findings of PA assessments.

3. Scope

The assessment tool is based on the six modules in the MQAS:

Module I	General requirements for procurement agencies
Module II	Prequalification
Module III	Purchasing
Module IV	Receiving and storage
Module V	Distribution
Module VI	Reassessment

The tool covers the topics each of the above-listed Modules below. The logical flow considered is the quality system and infrastructure of the PA under assessment, how the PA performed prequalification, then purchasing of the products followed by the

receiving and storage thereof. The last two modules then focus on the receiving of orders and dispatch of products followed by the reevaluation concept.

4. Assessment tool

The tool should be used by qualified, experienced persons when assessing a PA (including wholesalers and distributors) for compliance with recommended international standards. It can also be useful for a PA when doing a self-assessment.

The tool is not a checklist, but serves as a document to help and remind inspectors as to what should be assessed during inspections of PAs.

Module I: General requirements for procurement agencies

This Module covers general requirements for PAs including premises, equipment, transport and documentation (such as standard operating procedures (SOPs), confidentiality, code of conduct and complaint handling). Module I should be used in all cases of assessment of a procurement agency. (Modules II to VI may be used depending on the activities performed by the PA.)

Area of operation	Note	Critical aspects
Premises, equipment, furniture, transport	<p><i>General</i></p> <ul style="list-style-type: none"> • Licensed to operate • Sufficient space (offices for personnel, products, documents, samples, etc.) • Suitable conditions • Necessary furniture • Working office equipment • Stationery and consumables • Telephone and email access • Appropriate transport available 	<p>Compliance with legislation (licence)</p> <p>There must be a sufficient and functional infrastructure to enable the PA to perform its activities</p>

Table *continued*

Area of operation	Note	Critical aspects
Human resources	<p><i>Personnel</i></p> <ul style="list-style-type: none"> • Compliance with national legislation (e.g. responsible person) • Sufficient number of people • Key personnel – quality assurance, prequalification, purchasing, storage and distribution • Quality assurance/ prequalification and purchasing independent of one another • Support staff • Contracted personnel and agreements • Training, education and experience 	<p>Compliance with legislation</p> <p>Quality assurance/ prequalification and purchasing independent of one another (personnel and reporting structure)</p>
Organization	<p><i>Organization chart</i></p> <ul style="list-style-type: none"> • Authorized and current • In line with the job descriptions <p><i>Job descriptions</i></p> <ul style="list-style-type: none"> • Written job descriptions • Signed and dated 	
Ethical considerations	<p><i>Conflict of interest</i></p> <ul style="list-style-type: none"> • Policy on conflict of interest is observed • Signed declaration of interest <p>No vested interests</p> <p><i>Code of conduct</i></p> <ul style="list-style-type: none"> • Written, authorized and implemented • Covers conduct of personnel • All personnel to comply with a code of conduct <p><i>Confidentiality</i></p> <ul style="list-style-type: none"> • Relevant product information kept confidential • Confidentiality agreements exist 	Declaration and management of conflict of interest

Table *continued*

Area of operation	Note	Critical aspects
Computers	<p><i>Appropriate hardware and software</i></p> <ul style="list-style-type: none"> • Sufficient capacity and memory • Access control • Data transfer procedures • Reliable and accurate quality and management of data and information • Data storage (e.g. hard copies) • Back-up at defined intervals, storage, access, readable • Virus protection program and firewall • Technical support • Maintenance • Trained personnel 	If used, reliable data management (including access control)
Financial systems	<ul style="list-style-type: none"> • Adequate banking facilities • Signatories of bank accounts appointed • Accounting system in place • National and international financial transactions • Financial transactions performed without delay • Funds available • Regular financial audits are performed 	
Documentation	<p><i>Comprehensive documented system</i></p> <ul style="list-style-type: none"> • Covers policies, guidelines, norms, standards, manuals, procedures, records and related documents • SOPs for activities <p><i>Quality manual (QM)</i></p> <ul style="list-style-type: none"> • Contains a quality policy • Evidence of QM implementation, QM maintained, reviewed and amended as necessary 	Activities and responsibilities described in SOPs which are implemented and followed Records reflecting activities

Table continued

Area of operation	Note	Critical aspects
	<p><i>Standard operating procedures</i></p> <ul style="list-style-type: none"> • SOP for writing an SOP followed • Written, clear, detailed SOPs for activities • Controlled, distributed and retrieved when required • Available for use • SOPs are reviewed periodically • Quality risk management (QRM) principles applied 	
	<p><i>Style and layout</i></p> <ul style="list-style-type: none"> • SOPs in defined format • Signed and dated 	
<i>Activities to be covered by SOPs</i>	<p>All activities should be covered by SOPs and include:</p> <ul style="list-style-type: none"> • prequalification • purchasing • receiving and storage • distribution • training • handling of complaints • handling of recalls • document/record control including distribution and retrieval of SOPs • self-inspection • monitoring of environmental conditions (e.g. temperature) • monitoring of supplier performance • identifying and reporting SSFFC medical products • evaluating offers received • ordering product(s) from supplier or manufacturer • change control • variations • corrective and preventive action (CAPA) 	<p>Written SOPs followed for prequalification, purchasing, storage, distribution, complaints, recalls, identifying and reporting substandard/spurious/false-labelled/falsified/counterfeit (SSFFC) medical products</p> <p>Change control</p>

Table continued

Area of operation	Note	Critical aspects
List of prequalified products, manufacturers and suppliers	<ul style="list-style-type: none"> • Current, authorized, access-controlled list • Based on the outcome of evaluation • Contains required information • Product-, manufacturing site- and supplier-specific (where relevant) • A key person responsible 	A controlled list is maintained
Maintenance of records	<ul style="list-style-type: none"> • Records of all operations kept • Sufficient space for archiving • Access controlled • Retention period appropriate 	Records are available for review
Contract arrangements	<ul style="list-style-type: none"> • Written contracts for delegated activities 	Written, valid agreements in place

Module II: Prequalification

Prequalification is one of the key elements in ensuring purchase and supply of pharmaceutical products of acceptable quality. The prequalification process can be subdivided into two major parts, i.e. product-related assessment and manufacturer-related inspection.

Area of operation	Note	Critical aspects
Principles	<ul style="list-style-type: none"> • Documented policy and procedures for prequalification • Include assessment of product and manufacturers/suppliers • If delegated – written agreement in place 	

Table *continued*

Area of operation	Note	Critical aspects
Key persons and responsibilities	<ul style="list-style-type: none"> • Responsible personnel identified • Independent from the purchasing personnel • Job descriptions • Communication between personnel involved in evaluation and inspections <p data-bbox="384 546 711 600"><i>Evaluation of product information (evaluators)</i></p> <ul style="list-style-type: none"> • List of evaluators • Suitable qualifications and experience • Job descriptions • Contracted external evaluators used (confidentiality, conflicts of interest and financial resources, references) <p data-bbox="384 827 711 882"><i>Inspection of manufacturing sites (inspectors)</i></p> <ul style="list-style-type: none"> • List of inspectors • Job descriptions • Qualified, trained, experienced • Contracted inspectors – confidentiality and no conflict of interest 	Qualified, trained personnel perform prequalification activities (including assessment and inspections) Quality assurance/prequalification and purchasing independent of one another (personnel and reporting)
Key steps in prequalification defined	<p data-bbox="384 1090 663 1118"><i>Step 1: Soliciting information</i></p> <ul style="list-style-type: none"> • Procedures for preparation of detailed, clear specifications; soliciting information; receiving and processing of the information • Policy and procedure for handling late submissions • Recording of data received • Procedure for submitting product information publicly available and accessible • Product information to be submitted defined (as a minimum, see product questionnaire) 	Evaluation of product data and information as well as the criteria used to approve or reject a product Ensuring compliance with good manufacturing practices (GMP)

Table *continued*

Area of operation	Note	Critical aspects
	<i>Step 2: Receive product information</i>	
	<ul style="list-style-type: none"> • Written procedures for receiving, identification, marking files, containers and samples; and sufficient space for unpacking and storage • Procedure to ensure traceability of the product information • Personnel available 	
	<i>Step 3: Screen product information</i>	
	<ul style="list-style-type: none"> • SOP: screen for completeness • A screening form used • Record of screening kept • Outcome communicated to manufacturer/supplier 	
	<i>Step 4: Evaluate product information</i>	
	<ul style="list-style-type: none"> • Follow SOP for evaluation to check that the product meets requirements • Time frames • Evaluation report for each product exists • Outcome communicated to the manufacturer/supplier • Response invited where needed • Outcome accepted or rejected • Evaluation report kept as record • Samples analysed if needed (see also monitoring below) 	
	<i>Step 5: Plan, prepare and perform inspections</i>	
	<i>General points</i>	
	<ul style="list-style-type: none"> • Evidence of GMP compliance • Site of manufacture known • Site inspection policy • Contract manufacturing sites known • Control over active pharmaceutical ingredients (APIs) (inspection risk-based) 	

Table continued

Area of operation	Note	Critical aspects
	<i>Plan</i>	<ul style="list-style-type: none"> • SOP and recording system for inspection planning • Procedure and data reviewed as part of preparation for inspection (e.g. site master file)
	<i>Conduct</i>	<ul style="list-style-type: none"> • SOP: how to perform an inspection • Scope: data and information verified and WHO GMP compliance assessed • If not done – conditions for waiving on-site inspections
	<i>Inspection report</i>	<ul style="list-style-type: none"> • Inspection report for each site inspected • Outcome communicated • CAPA requested, received and reviewed • Conclusion or outcome • Copy of report kept
	<i>Step 6: Finalize assessment process</i>	<ul style="list-style-type: none"> • Written procedure followed • Covers product evaluation plus laboratory results and inspection outcome • Responsible persons (decision-taking) and reasons for decision • Outcome communicated • List of prequalified products, manufacturers and suppliers • Agreement between PA and supplier/manufacturer • List reviewed and updated at regular intervals
Cost recovery	<ul style="list-style-type: none"> • If used, transparent procedure • Fee-for-services structure 	

Module III: Purchasing

Procurement should be done with the aim of purchasing effective, quality assured products, and not focused on price alone. The term “procurement” in this Module relates specifically to the purchase of health sector goods from manufacturers or suppliers. The module goes on to describe the key activities in purchasing pharmaceutical products, as well as the recommended organizational structure of the procurement agencies which carry out these key activities.

Area of operation	Note	Critical aspects
Procurement strategies	<ul style="list-style-type: none"> • Policy: suppliers are selected and monitored through a process that takes into account product quality, service reliability and performance, delivery time, ethics, legal status, financial viability and minimum order quantities <p data-bbox="376 818 727 873"><i>Purchase prequalified products (from manufacturers/suppliers)</i></p> <ul style="list-style-type: none"> • Efficient and transparent management • Financial management procedures • Competitive procurement methods • Procedure to calculate lowest possible total cost • Procurement and purchasing procedures are transparent • Independent contract review • Purchasing and tender documents list all pharmaceutical products by their international nonproprietary name (INN) or national generic names • Intellectual property rights are respected in accordance with best practice and national law 	Purchasing prequalified products

Table continued

Area of operation	Note	Critical aspects
Procurement methods	<ul style="list-style-type: none"> • If they are responsive to the defined terms and conditions, responses are examined from invited suppliers • Adjudication procedure • Explicit criteria for awarding contracts • Informed of the outcome • Restricted tender • Prequalified products and suppliers • Competitive negotiation • Direct procurement 	<p>Adjudication procedure and related records</p> <p>Use a defined, transparent procurement method</p>
Key activities	<ul style="list-style-type: none"> • Develop a list or catalogue of products (INN) • Develop specifications for the products <p><i>Quantification</i></p> <ul style="list-style-type: none"> • Methods of product quantification • Quantities purchased based on reliable estimate <p><i>Procurement method</i></p> <ul style="list-style-type: none"> • According to the policy and procedures of the procurement agency 	
Organization and responsibilities	<ul style="list-style-type: none"> • Personnel with appropriate qualifications and training • Job descriptions • Independent from those responsible for prequalification and quality assurance • Procurement planned 	

Table *continued*

Area of operation	Note	Critical aspects
Monitoring of the performance of prequalified products, manufacturers and suppliers	<ul style="list-style-type: none"> • Procedure for continuous monitoring of the performance of products, manufacturers and suppliers <p data-bbox="384 468 623 495"><i>Monitoring may include:</i></p> <ul style="list-style-type: none"> • review of quality control results • verification that the product batches supplied have been manufactured in compliance with standards and specifications accepted in the product information through inspection • adverse events • random samples of batches supplied analysed (risk-based approach) • independent testing – reliable quality control laboratory (see selection criteria for quality control laboratory) • certificates of analysis available where appropriate • status of the laboratory (e.g. authorized, accredited) • handling of out-of-specification results • monitoring of complaints • outcome of inspection of manufacturing sites • outcome of reassessment of product information • monitoring of direct and indirect product costs • monitoring of adherence to delivery schedules • contract terms and conditions • tracking system (values of contracts awarded, total purchases, performance) 	Handling out-of-specification results Monitoring performance of products, manufacturers and suppliers and action taken by the PA in case of non-compliance
Donations	<ul style="list-style-type: none"> • Written procedure 	

Module IV: Receiving and storage

The PA should ensure that the pharmaceutical products purchased are received and stored correctly and in compliance with applicable legislation and regulations. Products should be received and stored in such a way that their quality and integrity is preserved, batch traceability is maintained and stock can be rotated.

Area of operation	Note	Critical aspects
General arrangements	<ul style="list-style-type: none"> • Received and stored correctly • Quality and integrity is maintained • Batch traceability • Stock rotation • Unidirectional flow • Security of materials and products • Subcontracting 	Procedures followed for receiving and storage Batch traceability
Pre-shipment quality control	<ul style="list-style-type: none"> • Batches released by the manufacturer (certificate of analysis (CoA)) • Batches additionally tested (risk-based approach) prior to shipment to PA • Selection criteria for quality control laboratory 	Batch release with CoA (meeting specifications)
Receiving of stock	<ul style="list-style-type: none"> • Receiving and dispatch bays • Incoming containers cleaned, quarantined • Review of CoAs • Released for use or distribution (responsible person involved) <p><i>Checks on receipt:</i></p> <ul style="list-style-type: none"> • order, delivery note, labels and transport conditions, integrity of packages and seals and for uniformity of the containers <p><i>Visual inspection for:</i></p> <ul style="list-style-type: none"> • contamination, tampering and damage, expiry date, compliance with labelling and packaging instructions • suspect containers and damaged containers – recorded and investigated 	Goods received and checked according to an appropriate SOP – supported by records Products released by responsible person

Table *continued*

Area of operation	Note	Critical aspects
Post-procurement control	<ul style="list-style-type: none"> • Random sampling for independent laboratory analysis • Selection criteria for quality control laboratory • SOP and national legislation • Representative samples – sampling plans and instructions (risk assessment) • Appropriately trained and qualified personnel 	Action taken in case of non-conforming product
Rejected materials	<ul style="list-style-type: none"> • SOP for rejected products • Separate storage or validated computerized system • Action approved by authorized personnel and recorded 	Rejected materials kept separately, access controlled and handled appropriately
Storage of materials/ products	<p><i>Personnel</i></p> <ul style="list-style-type: none"> • Trained • Personal hygiene and sanitation • Appropriate garments <p><i>Storage areas</i></p> <ul style="list-style-type: none"> • No unauthorized access • Sufficient space • Adequate ventilation, temperature and relative humidity • Conditions checked, monitored and recorded • Segregation of rejected, expired, recalled or returned stock • Toilet and washing facilities separated from storage areas • Narcotics/psychotropic medicines as per national legislation • SOP for fire control • No smoking or eating • SOP and records for cleaning • Waste management • Pest control • SOP for handling spillages 	Access controlled and sufficient space Appropriate conditions for storage

Table continued

Area of operation	Note	Critical aspects
	<p><i>Storage conditions</i></p> <ul style="list-style-type: none"> • As established by the manufacturer • Orderly, batch segregation, stock rotation, first expired-first out (FEFO) • Stored off the floor • Space to permit cleaning and inspection • Pallets in a good state of cleanliness and repair • Stacking of products without damage • Freeze-sensitive products – use monitoring devices • Cold rooms (qualification, temperature mapping, alarm, monitoring, records, back-up system in case of failure) 	
	<p><i>Monitoring of storage conditions</i></p> <ul style="list-style-type: none"> • Temperature mapping protocol and report • Calibrated sensors/devices • Ongoing monitoring with records • Out-of-limit and out-of-trend results investigated, action taken 	
	<p><i>Miscellaneous and hazardous materials</i></p> <ul style="list-style-type: none"> • Rodenticides, insecticides, fumigating agents and sanitizing materials • Toxic substances and flammable materials 	
Re-packaging and re-labelling	<ul style="list-style-type: none"> • If performed – in compliance with national legislation and WHO GMP 	Compliance with national legislation and WHO GMP

Table *continued*

Area of operation	Note	Critical aspects
Stock control	<ul style="list-style-type: none"> • Validated stock control system • Batch number control and expiry dating • Periodic stock reconciliation • Significant stock discrepancies investigated • Records maintained • Damaged containers handled <p><i>Control of obsolete and outdated materials and products</i></p> <ul style="list-style-type: none"> • SOP • Regular checks <p>Recalled materials and products</p> <ul style="list-style-type: none"> • SOP • Written records of actions with signatures • Products identified, recorded, reconciled and stored separately • Decision by appropriately qualified and experienced member of staff <p><i>Returned goods</i></p> <ul style="list-style-type: none"> • SOP • Quarantined and assessed • Resale conditions • Destruction in compliance with national requirements • Records <p><i>Waste materials</i></p> <ul style="list-style-type: none"> • SOP • Safe storage while awaiting disposal • Toxic substances and flammable materials • No accumulation • Safe disposal, national regulations 	Stock control in place (e.g. reconciliation, obsolete materials, recalled products, returned goods, FEFO and waste)

Table continued

Area of operation	Note	Critical aspects
Documentation: written instructions and records:	<ul style="list-style-type: none"> • SOPs for activities • Handling of expired stock • Ensuring batch traceability • Records for storage conditions, precautions • National regulations concerning labels and containers • Comprehensive records of all activities • Retention of records 	Record-keeping ensuring traceability (e.g. receiving, issuing, expired goods)

Module V: Distribution

The PA (or contracted party) should have a well-managed distribution system meeting the objectives of ensuring constant supply of quality medicines. Distribution should be done in accordance with general principles of GMP.

Area of operation	Note	Critical aspects
General	<ul style="list-style-type: none"> • Constant supply of medicines • Minimize medicines losses (spoilage and expiry) • Accurate inventory records • Prevent theft and fraud 	
Transport conditions	<ul style="list-style-type: none"> • Transport process has no negative impact on product • Required storage conditions maintained • Temperature excursions – risk assessment 	Appropriate transport conditions

Table continued

Transport conditions	Note	Critical aspects
Cold chain	<ul style="list-style-type: none"> • Validated process • Applied where needed • Appropriate containers • Packaging procedure • Cooling agents used • Calibrated monitoring devices • Monitoring records reviewed, maintained 	Cold chain validated, maintained and monitored
Dispatch procedures	<ul style="list-style-type: none"> • Compliance with legislation • Authorized recipients • Procedures in place • Special packaging requirements observed where needed • Dispatch and transport after receipt of a delivery order 	Compliance with legislation Authorized recipients
Dispatch containers	<ul style="list-style-type: none"> • Provide protection • Appropriately labelled • Prevent theft (e.g. locked/wrapped) 	
Dispatch records	<ul style="list-style-type: none"> • Detailed records kept (e.g. date, customer name and address; product name and batch number and quantity) • Products and batches traceable • Discrepancies investigated 	Records ensure traceability of goods
Port of entry	<ul style="list-style-type: none"> • Storage conditions met • Temperature-sensitive products handled appropriately • Security measures in place (e.g. prevent theft, fraud and bribery) 	

Module VI: Reassessment

Quality of products and services should be continuously monitored. This process includes reassessment.

Area of operation	Note	Critical aspects
Reevaluation of manufacturers	<ul style="list-style-type: none">• Reinspection frequency based on risk assessment• Within five-year cycle• Change control• Mechanism for suspension and withdrawal	Reinspection policy and procedure followed
Reevaluation of products	<ul style="list-style-type: none">• Reevaluation procedure• Within five-year cycle• Variations procedure	Reevaluation of product policy and procedure followed
Monitoring performance of contractors	<ul style="list-style-type: none">• Written procedure• Covers continuous monitoring, periodic review and renewal of contracts• System for documenting service problems	Procedure followed for monitoring performance

Further reading

1. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-First Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943; https://iris.who.int/bitstream/handle/10665/43632/WHO_TRS_943_eng.pdf?sequence=1&isAllowed=y) Annex 3.
2. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981; https://iris.who.int/bitstream/handle/10665/81144/WHO_TRS_981_eng.pdf?sequence=1&isAllowed=y), Annex 3.
3. WHO Recommendations for quality requirements when plant – derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-Ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992; https://iris.who.int/bitstream/handle/10665/176954/9789240693968_eng.pdf?sequence=1&isAllowed=y), Annex 6.
4. WHO general guidance on variations to multisource pharmaceutical products. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifties Report* Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996; <https://iris.who.int/bitstream/handle/10665/255338/9789241209960-eng.pdf?sequence=1&isAllowed=y>), Annex 10.

Revision history

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
1. WHO good manufacturing practices: main principles for pharmaceutical products			
1.1	WHO good manufacturing practices for pharmaceutical products: main principles. Annex 2, WHO Technical Report Series, 986	2014	No change
1.2	WHO good manufacturing practices: guidelines on validation. Annex 3, WHO Technical Report Series, 1019	2019	Replaces - WHO Supplementary guidelines on good manufacturing practices: validation. Annex 4, WHO Technical Report Series, 937; 2006
1.3	Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation. Annex 2, WHO Technical Report Series, 1033	2021	New guideline
1.4	Good manufacturing practices: water for pharmaceutical use. Annex 3, WHO Technical Report Series, 1033	2021	Replaces - WHO good manufacturing practices: water for pharmaceutical use. Annex 2 WHO Technical Report Series, 970; 2012
1.5	Production of water for injection by means other than distillation. Annex 3, WHO Technical Report Series, 1025	2020	New guideline
1.6	Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Annex 8, WHO Technical Report Series, 1010	2018	No change

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
1. WHO good manufacturing practices: main principles for pharmaceutical products <i>continued</i>			
1.7	Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products - Part 2: Interpretation of <i>Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products</i> . Annex 2, WHO Technical Report Series, 1019	2019	New – interpretation of Annex 8, WHO Technical Report Series, 1010: 2018
2. WHO good manufacturing practices: starting materials			
2.1	WHO good manufacturing practices for active pharmaceutical ingredients (bulk drug substances). Annex 2, WHO Technical Report Series, 957	2010	No change
2.2	Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients. Annex 5, WHO Technical Report Series, 885	1999	No change <i>NB: Text under revision</i>
3. WHO good manufacturing practices: specific medical products			
3.1	WHO good manufacturing practices for sterile pharmaceutical products. Annex 2, WHO Technical Report Series, 1044	2022	Replaces - WHO good manufacturing practices for sterile pharmaceutical products. Annex 6, WHO Technical Report Series, 961; 2011
3.2	WHO good manufacturing practices for biological products (jointly with the Expert Committee on Biological Standardization). Annex 3, WHO Technical Report Series, 996	2016	No change

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
3. WHO good manufacturing practices: specific medical products <i>continued</i>			
3.3	WHO guidelines on good manufacturing practices for blood establishments (jointly with the Expert Committee on Biological Standardization). Annex 4, WHO Technical Report Series, 961	2011	No change
3.4	WHO good manufacturing practices for medicinal gases. Annex 5, WHO Technical Report Series, 1044	2022	New guideline
3.5	International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceutical products. Annex 2, WHO Technical Report Series, 1025	2020	Replaces – Guidelines on good manufacturing practices for radiopharmaceutical products. Annex 3, WHO Technical Report Series, 908; 2003
3.6	Guidelines on good manufacturing practices for the manufacture of herbal medicines. Annex 2, WHO Technical Report Series, 1010	2018	No change
3.7	WHO good manufacturing practices for pharmaceutical products containing hazardous substances. Annex 3, WHO Technical Report Series, 957	2010	No change
3.8	WHO good manufacturing practices for investigational products. Annex 7, WHO Technical Report Series, 1044	2022	Replaces – Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans. Annex 7, WHO Technical Report Series 863; 1996

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
3. WHO good manufacturing practices: specific medical products <i>continued</i>			
3.9	IAEA - WHO guideline on good manufacturing practices for investigational radiopharmaceutical products. Annex 3, WHO Technical Report Series, 1044	2022	New guideline
4. Related guidelines			
4.1	WHO good practices for research and development facilities of pharmaceutical products. Annex 6, WHO Technical Report Series, 1044	2022	New guideline
4.2	WHO guidelines for drafting a site master file. Annex 14, WHO Technical Report Series, 961	2011	No change
4.3	Guidelines for the preparation of a contract research organization master file. Annex 7, WHO Technical Report Series, 957	2010	No change
4.4	WHO guidelines on technology transfer in pharmaceutical manufacturing. Annex 6, WHO Technical Report Series, 1044	2022	Replaces – WHO guidelines on technical transfer in pharmaceutical manufacturing. Annex 7, WHO Technical Report Series, 961; 2011
4.5	WHO guidelines on quality risk management. Annex 2, WHO Technical Report Series, 981	2013	No change
4.6	Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. Annex 6, WHO Technical Report Series, 1025	2020	New guideline

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
4. Related guidelines <i>continued</i>			
4.7	Guideline on data integrity. Annex 4, WHO Technical Report Series, 1033	2021	Replaces - Guidance on good data and record management practices. Annex 5, WHO Technical Report Series, 996; 2016
4.8	General guidance on hold-time studies. Annex 4, WHO Technical Report Series, 992	2015	No change
4.9	Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. Annex 10, WHO Technical Report Series, 1010	2018	No change
4.10	WHO guidelines for sampling of pharmaceutical products and related materials. Annex 4, WHO Technical Report Series, 929,	2005	No change
4.11	Guidelines on packaging for pharmaceutical products. Annex 9, WHO Technical Report Series, 902	2002	No change
4.12	Guidelines on the implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. Annex 9, WHO Technical Report Series, 1033	2021	Replaces – Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. Annex 10, WHO Technical Report Series, 863; 1996
4.13	Good storage and distribution practices for medical products. Annex 7, WHO Technical Report Series, 1025	2020	Replaces - Guide to good storage practices for pharmaceuticals, Annex 9, WHO Technical Report Series, 908; 2003

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
4. Related guidelines <i>continued</i>			
4.14	Good trade and distribution practices for pharmaceutical starting materials. Annex 6, WHO Technical Report Series, 996	2016	No change
4.15	Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products. Annex 9, WHO Technical Report Series, 961	2011	No change
4.16	Technical supplements to Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products. Annex 5, WHO Technical Report Series, 992	2015	No change
4.17	WHO guidelines on good herbal processing practices for herbal medicines. Annex 1, WHO Technical Report Series, 1010	2018	No change
5. Laboratory guidelines			
5.1	WHO good practices for pharmaceutical quality control laboratories. Annex 1, WHO Technical Report Series, 957	2010	No change <i>NB: Text under revision</i>
5.2	WHO good practices for pharmaceutical microbiology laboratories. Annex 2, WHO Technical Report Series, 961	2011	No change
5.3	Good chromatography practices. Annex 4, WHO Technical Report Series, 1025	2020	New guideline

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
5. Laboratory guidelines <i>continued</i>			
5.4	WHO guidelines for preparing a laboratory information file. Annex 13, WHO Technical Report Series, 961	2011	No change
6. Inspections			
6.1	Quality management system requirements for national inspectorates. Annex 5, WHO Technical Report Series, 1025	2020	Replaces - WHO Quality systems requirements for national good manufacturing practice inspectorates. Annex 8, WHO Technical Report Series, 902; 2002
6.2	Provisional guidelines on the inspection of pharmaceutical manufacturers. Annex 2, WHO Technical Report Series, 823	1992	No change
6.3	Guidance on good manufacturing practices: inspection report. Annex 4, WHO Technical Report Series, 996	2016	No change
6.4	Guidelines on pre-approval inspections. Annex 7, WHO Technical Report Series, 902	2002	No change
6.5	Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. Annex 9, WHO Technical Report Series, 1010	2018	No change

No.	Document and reference	Publication date	Revision history (changes to the 9 th edition)
6. Inspections <i>continued</i>			
6.6	Assessment tool based on the model quality assurance system for procurement agencies: aide-memoire for inspection. Annex 4, WHO Technical Report Series, 986	2014	No change

The background of the image is filled with a large number of white, circular pharmaceutical tablets, some with embossed markings, creating a dense, textured pattern.

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Website: <https://www.who.int/teams/health-product-policy-and-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals>

ISBN 9789240086081



9 789240 086081