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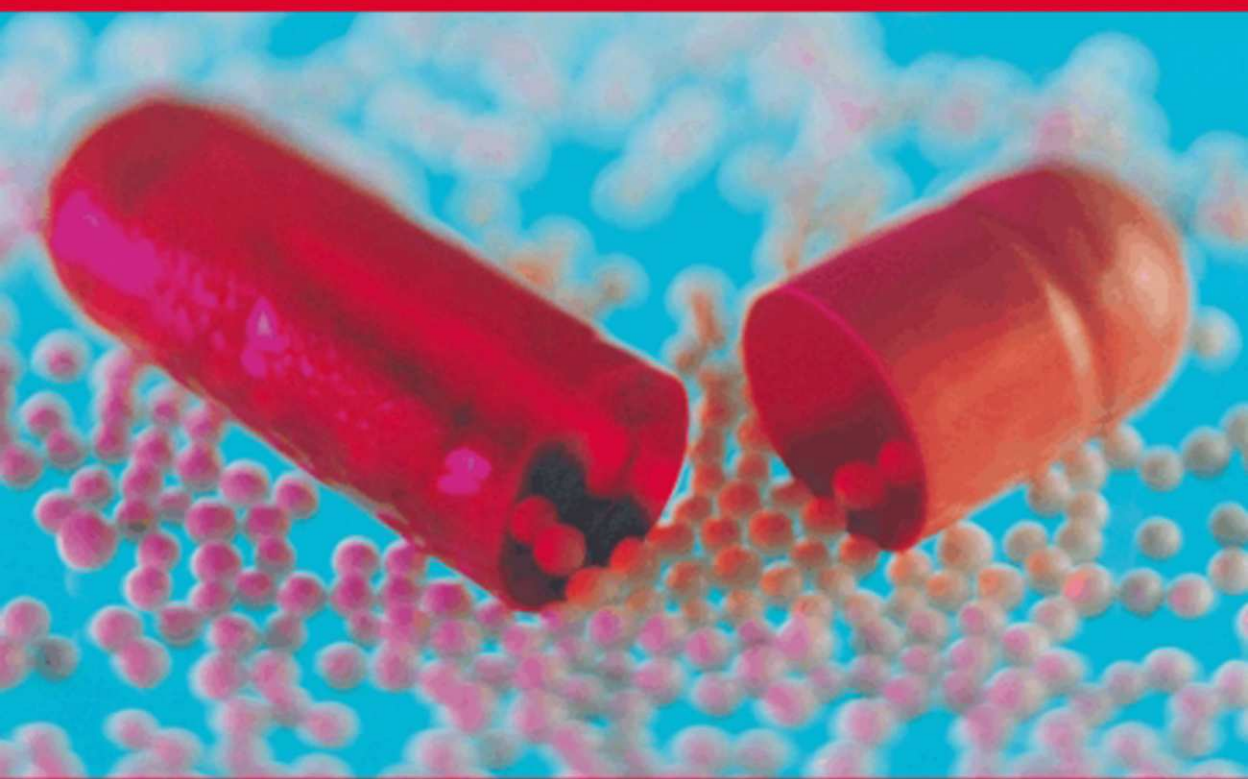
Quality



Kate McCormick

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Quality

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Pharmaceutical Engineering Series

Kate McCormick

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Abbreviations

AAPS	American Association of Pharmaceutical Scientists
ABS	acrylonitrile butadiene styrene
ADR	adverse drug reaction
AIDS	acquired immune deficiency syndrome
ANDA	abbreviated new drug application
API	active pharmaceutical ingredient
BOD	biological oxygen demand
BS	British Standard
BSI	British Standards Institute
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDI	continuous electrodeionization
CEEC	Central or Eastern European Country
CEN	Comité Européen de Normalisation
CFR	code of federal regulations
cfu	colony forming units
cGMPs	current good manufacturing practices
CIP	clean-in-place
CIS	Commonwealth of Independent States
COD	chemical oxygen demand
CPD	continuing professional development
CPMP	Committee for Proprietary Medicinal Products
CVMP	Committee for Veterinary Medical Products
DHSS	Department of Health and Social Security
DQ	design qualification
EC	European Community
EDI	electrodeionization
EEC	European Economic Community
EFPIA	European Federation of Pharmaceutical Industries' Associations
EFTA	European Free Trade Association
EMEA	European Medicines Evaluation Agency
EPA	Environmental Protection Act
ETO	ethylene oxide
EU	European Union

EudraNet	European Union Drug Regulatory Network
FDA	US Food and Drug Administration
FEFO	first expired, first out
FIFO	first in, first out
GCP	good clinical practice
GDP	good distribution practice
GCLP	good control laboratory practice
GLP	good laboratory practice
GMP	good manufacturing practice
GRP	glass reinforced plastic
HEPA	high-efficiency particulate air
HR	human resources
ICH	International Conference on Harmonisation
IFPMA	International Federation of Pharmaceutical Manufacturers Associations
IQ	installation qualification
ISO	International Standards Organization
ISPE	International Society for Pharmaceutical Engineering
IT	information technology
JPMA	Japan Pharmaceutical Manufacturers' Association
JUSE	Union of Japanese Scientists and Engineers
LIFO	last in, first out
LIMS	laboratory information management system
LVP	large volume parenterals
MCA	Medicines Control Agency
MCC	Medicines Control Council
MHW	Ministry of Health and Welfare (Japan)
MNC	multinational company/multinational corporation
MRL	maximum residue limit
NAFTA	North American Free Trade Area
NCE	new chemical entity
NDA	new drug application
NGT	nominal group technique
OPPI	Organization of Pharmaceutical Producers of India
OQ	operational qualification
OTC	over the counter
PhRMA	Pharmaceutical Research and Manufacturers of America
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PMA	Pharmaceutical Manufacturers Association
ppm	parts per million
PQ	performance qualification/process qualification
PR	public relations
PTFE	polytetrafluoroethylene
PVC	polyvinyl chloride
PVDF	polyvinylidene fluoride
QA	quality assurance
QC	quality control
QP	qualified person

QSIT	quality systems inspection technique
QWP	quality working party
R & D	research and development
RO	reverse osmosis
RP	responsible person/responsible pharmacist (in France)
SIP	steam-in-place
SOP	standard operating procedure
SVP	small volume parenterals
TGA	Therapeutic Goods Administration
TQM	total quality management
UMIST	University of Manchester, Institute of Science and Technology
USP	US Pharmacopoeia
UV	ultraviolet
VMP	validation master plan
WFI	water for injection/water for injections
WHO	World Health Organization

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1

Quality life cycle

1.1 Introduction

Within the pharmaceutical industry, quality is the key issue that has to be addressed above all others. It is the reason that so many regulations, guidelines and controls are important. This volume deals with quality in its widest sense, reviewing international systems such as the (International Standards Organization) ISO 9000 and ISO 14000 series of standards and generic instruments such as total quality management and the cost of quality, which are applicable across all industries in addition to industry-specific topics such as good manufacturing practice (GMP).

In this first chapter, an overview is presented of quality at all the stages of the pharmaceutical life cycle. There is then an overview of quality considerations relating specifically to research and development, including good laboratory practice (GLP) and good clinical practice (GCP). There is a discussion of the mechanisms that are in place, both in Europe and the USA, to ensure that only pharmaceuticals of the appropriate quality are distributed to the patient. Brief mention is made of the quality considerations relating to manufacturing, although GMP is a large enough topic to be covered on its own (see Chapter 4). Similarly, the quality considerations relating to logistics and distribution are briefly reviewed in this chapter, but good distribution practice (GDP) is fully covered elsewhere (see Chapter 5). Finally, there follows a discussion on the systems used by companies to manage defective products, either via complaints or recalls.

1.2 Research and development

Before a new drug can be marketed, there are a number of lengthy processes that must be gone through, which may be loosely combined under the heading of research and development (R&D). This section summarizes the processes, which are essentially the same in Europe and the USA, and which take somewhere between eight and ten years to complete for a completely new molecule.

In November 2001, many of the EU directives relating to medicinal products for human use, which are referred to in this volume, were brought together in Directive 2001/83/EC. This was a consolidation exercise only, with no implications for the content of the earlier directives.

1.2.1 Pre-clinical studies

When a new chemical entity (NCE) is discovered, it is initially subjected to a number of pre-clinical research activities. First of all, it is tested both *in vitro* and *in vivo* to determine whether there is a beneficial biological activity and whether that activity can be enhanced by modifying the molecule in any way.

Toxicology studies

A critical part of the pre-clinical work is the toxicological investigation of safety aspects of the molecule. There are very few drugs that can be said to cause no adverse reaction at all. However, a judgement has to be made as to whether the benefits of a drug outweigh the potential side effects. There are a number of different types of toxicological studies that must be carried out, depending on the type of drug:

- Acute toxicity: carried out over two weeks in three to four species to determine the maximum tolerated dose.
- Subacute toxicity: carried out over six months in two species.
- Chronic toxicity: carried out over a maximum of 12 months in rats and one other species to see if there are any adverse effects resulting from repeated daily doses.
- Reproductive toxicity: carried out over a maximum of nine months in two species to identify any adverse effects on fertility and reproductive abilities.
- Mutagenic toxicity: carried out over 18–24 months under both *in vitro* and *in vivo* conditions.

This stage of the R & D cycle can take several years and will need to be completed before a company can obtain approval to carry out clinical studies.

Pre-formulation studies

Pre-formulation studies need to be carried out in order to determine the physicochemical characteristics of the molecule and thus the most appropriate dosage forms that can be used. Studies will include some or all of the following:

- Spectroscopy: to identify a basic analytical method.
- Solubility: in relation to liquid dosage forms and to identify the most appropriate salt to work with.
- Melting point: to determine crystalline solubility.
- Assay development: using more sophisticated equipment and related to drug stability studies.
- Stability: in both liquid and solid dosage forms.
- Microscopy: to identify particle size and crystal formation.
- Powder flow and compression properties: in relation to dry product dosage forms.
- Excipient compatibility: to ensure that the final dosage form will perform correctly.

Once the pre-formulation studies have been completed, the most appropriate dosage form can be determined, based on such factors as the purpose for which the drug is intended and the physicochemical characteristics of the chemical entity.

Biopharmaceutical studies

As part of the process of finalizing the dosage form, it is necessary to carry out biopharmaceutical studies in order to ensure that the drug reaches the part of the body where it is required, and is maintained at the right concentration for the right period of time. This includes identification of the appropriate dosage levels and frequency. These studies relate to four stages, called ADME for short:

- Absorption: how the drug enters the body and reaches the bloodstream.
- Distribution: how the drug travels through the body.
- Metabolism: the way in which the drug is changed by the body.
- Elimination: how the drug leaves the body.

The amount of drug that reaches the bloodstream, and the speed at which it takes place is called its bioavailability. It is generally measured by means of pharmokinetic plasma studies of drug concentration against time.

Stability studies

Pre-clinical studies of the final dosage form will extend to include stability studies relating to the primary and secondary packaging materials that are planned to be used. These studies examine the physical, chemical or microbiological deterioration of the drug over time in order to determine the appropriate shelf life that can be guaranteed.

Since stability or rather, lack of stability, is something that develops over time, it could take years to complete these studies if they were all conducted under a 'real-time' basis. As an alternative to this, accelerated stability studies can be used, in which the packs are exposed to extremes of conditions such as heat, light and moisture. Results thus obtained can then be converted to equivalents for ambient conditions.

1.2.2 Clinical studies

Assuming that the pre-clinical studies, particularly the toxicological tests, have produced acceptable results, the company will seek permission from the appropriate regulatory body to carry out clinical studies. The extent of the trials will depend on the nature of the drug and its proposed application. The trials are generally carried out in a number of stages.

Phase I trials

These are carried out over a period of three to six months and involve a group of around 100 healthy volunteers. Each subject receives a small dose of the drug and is then monitored for physiological reactions.

Phase II trials

These are carried out on patients, since the activity of the drug in healthy subjects may be different to that in subjects suffering from the disease for which the drug is intended. The trials last over a period of between six months and two years, and involve hundreds of subjects.

The objectives of Phase II trials are to determine whether the drug is effective or not, to identify the extent of any adverse reactions and to confirm the most effective dosage routine.

There are three types of trial that can be carried out:

- Open trials: in which the patient knows whether they are receiving the trial drug or a placebo.
- Single blind trials: in which the patient does not know whether they are receiving the trial drug or a placebo.
- Double blind trials: in which neither the patient nor the trial administrators know whether the trial drug or a placebo has been administered.

Phase III trials

These trials are also carried out using patients, but the size of the trial population is much larger (hundreds or even thousands of subjects) and the length of the trial is greater than in Phase II (lasting for anything up to five years).

The purpose of these trials is to confirm the effectiveness and expected adverse reactions over a much larger group of subjects. In addition, it is the opportunity to study the interaction of the drug with any other medication that the patients might be taking and to confirm the appropriate dosage regime for different groups of patients, such as children or the elderly.

On completion of the clinical trials, the company may submit their application for a marketing licence for the drug in question.

1.3 Good laboratory practice (GLP)

Both in Europe and in the USA, the conduct of pre-clinical studies is controlled by a variety of regulations and guidelines known collectively as good laboratory practice. Essentially, this is the control of non-clinical (generally animal) studies carried out in support of a research or a marketing application, in order to evaluate product safety or biocompatibility.

1.3.1 GLP in Europe

GLP requirements within the European Union (EU) are covered in Section II of the annex to Council Directive 87/18/EEC, which was amended by Commission Directive 1999/11/EC. As with other legislation, the individual member countries develop their own measures for implementation, although these are often harmonized across the EU. As an example of how this is applied in Europe, the next section reviews GLP legislation within the UK.

1.3.2 GLP in the UK

The UK GLP regulations were published in their latest format as The Good Laboratory Practice Regulations 1999. It consists of ten main sections as follows:

- Test facility organization and personnel: dealing with the management and personnel issues including job descriptions and training records.

- Quality assurance (QA) programme: dealing with the requirement for an independent QA programme, with personnel who are not involved in the studies, to ensure that GLP is complied with.
- Facilities: ensuring that adequate facilities are available to allow the studies to be carried out without the results being compromised in any way by lack of space or cross-contamination.
- Apparatus, materials and reagents: covering the validation, maintenance and storage of equipment and chemicals.
- Test systems: covering both physicochemical and biological testing systems.
- Test and reference items: dealing with the receipt, handling, sampling and storage of all test and reference materials.
- Standard operating procedures (SOPs): listing the main areas of activity that should be covered by SOPs, together with the change control requirements for the system.
- Performance of the regulatory study: dealing with the development of a study plan and also with its execution.
- Reporting of regulatory study results: covering the contents and layout of the study report.
- Storage and retention of records and materials: dealing with what should be archived and how those archives should be kept.

As part of the same document, there is a guideline for the inspection of test facilities. There is a chapter for each of the sections listed above, detailing what should be inspected, why and how.

The same guideline also covers auditing of specific studies. These may be part of a facility inspection or carried out independently at the request of the regulatory authority. They include a comparison of the final report with the original study plan, plus a review of SOPs and other documents.

1.3.3 GLP in the USA

GLP regulations and guidelines were first drafted by the US Food and Drug administration (FDA) in the mid-1970s. They were updated in April 1993 and form Part 58 of Code of Federal Regulations Title 21, chapter 1.

Essentially the same material is covered in the US GLP as in the UK version but it is phrased in a different format, covering 36 different clauses. These are numbered in numerical order, but not sequentially. For example, clause 58.15 deals with inspection of a testing facility, whilst clause 58.35 deals with the requirement for a quality assurance unit.

1.4 Good clinical practice (GCP)

The concept of GCP was first established during the 18th World Medical Assembly in Finland in 1964. The so-called Declaration of Helsinki was subsequently amended in later Assemblies in Japan in 1975, in Italy in 1983, in Hong Kong in 1989 and in South Africa in 1996. The declaration is entitled ‘Recommendations Guiding Physicians in Biomedical Research involving Human Subjects’.

The declaration contains 12 basic principles in relation to the conduct of clinical trials using humans:

- The trial should be based on good scientific investigation including pre-clinical studies.
- The design and conduct of the studies should be independently scrutinized by bodies unconnected with the investigator or the sponsor.
- Responsibility for the study must lie with a medically qualified person. The subject must never take responsibility.
- The perceived benefits of the study must be in proportion to the anticipated risk.
- The study must always be preceded by a risk/benefit analysis and the interests of the subject must always take precedence.
- The physical and mental integrity of the subject, together with their privacy, should always be protected.
- Studies should only be carried out if the risks are predictable. If the risks are found to be greater than anticipated, the study should be stopped.
- Study results should always be reported (or published) accurately.
- The subjects should be fully informed of the details of the study, the potential risks and benefits, their right to refuse to take part or withdraw at a later date. They should be asked to provide written informed consent.
- Professional relationships between subjects and their physicians should not be allowed to influence the process of informed consent.
- In the case of a minor, informed consent is required from the legal guardian.
- The protocol (i.e. plan) for the study should include ethical considerations and a statement of compliance to the principles of GCP.

The declaration continues with some points on combining medical research with professional care, i.e. the use of clinical trials drugs to treat sick people, and the use of healthy volunteers for non-therapeutic trials.

1.4.1 GCP in the USA

Within Title 21 of the FDA Code of Federal Regulations, clinical trials are covered by parts 50, 54 and 56. Part 50 deals with the protection of human subjects and in particular, the issue of informed consent. Part 54 deals with the disclosure of financial aspects of clinical investigations. Part 56 covers the topics of Institutional Review Boards, their make-up, how they operate and their key responsibilities.

Since the USA is one of the signatories of the International Conference on Harmonisation (ICH), the organization and conduct of clinical trials is governed by the ICH guidelines. (See Section 1.4.3 below for a discussion of the GCP guidelines and Chapter 11 for a full explanation of ICH.)

1.4.2 GCP in Europe

The Clinical Trials Directive was developed within Europe over a ten-year period, from 1991. It was finally published in the *Official Journal of the European Communities* in May

2001. By May 2004, all Member States must have made the necessary changes to legislation and implemented the requirements of the Directive.

The Directive is aimed at regulation of clinical trials, including multi-centre trials carried out within the EU. It closely reflects the content of the ICH guidelines (see below). The principles and definitions are followed by sections on the protection of trial subjects, the commencement of a clinical trial, exchange of information, manufacture and labelling of clinical trials materials, compliance and reporting of clinical safety data.

There are a number of major implications arising out of the Clinical Trials Directive. The requirements for authorization from both the competent authority and the ethics committee are extended to cover all trials, including Phase I studies. This was not previously the case in the UK in particular and more than 50 per cent of the Phase I trials performed worldwide were being carried out in the UK. The time-limit in which a request for an authorization must be dealt with has been reduced, so that the initiation of trials should be speeded up as a result.

There are a number of implications for the protection of the patient, with a strengthening of the requirements for informed consent and also the reporting of adverse events and termination of studies.

From a manufacturing point of view, the most significant implication is that all clinical trials materials must be manufactured under GMP conditions. Importing clinical trials materials will require an authorization and the services of a qualified person (QP) who will keep a register of batches. For major pharmaceutical companies and those involved in manufacturing of licensed products, neither of these requirements is likely to be a problem. However, for small companies producing only clinical trials materials and academic establishments carrying out Phase I trials only, this is a significant requirement that will inevitably result in an increase in costs.

1.4.3 ICH guidelines on GCP

The purpose of this standard is to agree a unified approach for use by the USA, the EU and Japan. This is to facilitate mutual acceptance of clinical studies data by the regulatory authorities in each country.

The guideline is part of a family of documents related to efficacy, numbered E1 to E12 within the ICH indexing system:

- E1: exposure
- E2: clinical safety
- E3: study reports
- E4: dose responses
- E5: ethnic factors
- E6: GCP guidelines
- E7: special populations
- E8–E10: clinical trial design
- E11: paediatrics
- E12: therapeutic categories.

The GCP guidelines are divided into eight main chapters. After the introduction, glossary and a review of the principles of GCP, there is a section on the responsibilities

and operation of Institutional Review Boards and Independent Ethics Committees. This is followed by a chapter on the investigator, dealing with such aspects as the requirements for a qualified person, the organization and the conduct of the trials.

The next chapter deals with the role of the sponsor and covers aspects such as quality assurance, provision of clinical trial material and monitoring of the studies. This is followed by a chapter on the design of clinical trials and the writing of protocols.

The investigator's brochure is covered in the next chapter. This is a document that is produced to help the potential investigators understand the purpose of the trial. It contains a review of the pre-clinical and clinical data that have been obtained previously.

The final chapter deals with the essential documents that are required both before and during a clinical trial.

It can be seen from the above that the GCP guideline covers all the aspects raised in the original Declaration of Helsinki, and thus acts as a major control on the quality of clinical studies and the protection of human subjects.

1.4.4 Manufacture of clinical trials material

The manufacture of pharmaceuticals for dispensing during a clinical trial is not covered by the same legislative requirements as a licensed drug. By definition, the product is to be used in the studies that are carried out to compile a registration application dossier and hence cannot already have a marketing authorization in place. It is generally accepted, however, that the manufacture of the clinical trial material should be subject to the same GMP requirements as licensed products. In addition, there are guidelines that apply specifically to such 'investigational medicinal products'.

Quality management and personnel

Annex 13 of the EU GMP guidelines covers the additional aspects involved in the manufacture of these products. Following the introduction and a glossary, there is a section covering a number of the normal GMP chapters and highlighting the specific differences. In the section on quality management it draws attention to the fact that validation will be less developed than for licensed products, that processes may be variable from batch to batch, and the importance of self-inspections and independent audits.

The section on personnel acknowledges the fact that there are likely to be only a small number of personnel involved, but emphasizes the importance of maintaining the independence of QC from production.

Premises and equipment

The section on premises and equipment recognizes the fact that manufacturing of clinical trials materials can differ from the production of licensed materials in the same way as the manufacturing of 'specials' (see Section 1.7 below). The batch size is small and it is likely that different products could be in progress in different parts of the same facility at the same time. This has implications for product security systems and for cleaning procedures in order to ensure that no cross-contamination occurs.

There is an additional consideration in relation to the manufacture of highly sensitizing or biological products. Under GMP requirements, such products would normally be

produced in separate facilities. However, at the stage of clinical trials, this is not practical. An acceptable alternative would be the use of campaign manufacture, but particular care needs to be taken with cleaning and product security systems.

Finally, the small batch sizes involved cause problems in the validation of sterile manufacturing processes. The required number of units will often be equivalent to a full batch. The fact that many operations could be manual will increase the need for environmental monitoring.

Documentation

The section on documentation deals with the fact that the process may change during the time of the trial and hence it is important to have a good change control procedure to ensure full traceability of all the changes. In these circumstances, it is not essential to develop formal master formulation or processing instructions, as it would be for licensed products.

Documentation should be stored for at least two years after the completion or discontinuation of the trial. The documentation specifically covered includes:

- The order, which is made by the trial sponsor to a clinical trials material manufacturer.
- The product specification file, which contains all the information required to carry out manufacturing, packaging and release.
- The master formulation or processing instructions, which must contain details of all changes that have taken place, with a full change history.
- Packaging instructions, which are likely to be more complex than for a licensed product and hence have increased requirements for quality control checks and reconciliation.
- Labelling instructions, which includes a list of the information that must be included on the primary and secondary packaging.
- Manufacturing and packaging records, which need to contain sufficient detail to allow full batch traceability.

Production

The section on production begins with a comment on the implications of possible variations in starting materials. It then continues with a discussion on manufacturing operations. There is a review of the fact that, owing to the lack of validation, there will tend to be less information from which to determine critical process parameters. It may be necessary to deduce process parameters from information obtained on other systems. The need for reconciliation is emphasized, particularly in relation to labelling. Additionally, there is mention of the increased levels of quality control checks that may be required in relation to biological contamination, cleaning procedures and unvalidated processes such as mixing.

There is a review of the considerations to be made in the manufacture of clinical trial material for comparator product studies. It is important that the integrity of the product is maintained and the significance of any changes is recognized. Changes to the primary packaging used may have an effect on the use-by date that can be applied.

There is also a mention of the aspects of randomization codes and blinding operations. It is important that identification of the ‘blinded’ product is possible and that appropriate samples are kept.

Quality control

The section on quality control emphasizes the increased importance of end-product testing in the absence of validated processes. There is acknowledgement of the need for compliance with the aspects of the specification that relate to efficacy. Retained samples of clinical trial material should be kept for shelf life plus one year, or two years after completion of the trial, whichever is the longer. These samples will generally be kept in the same primary packaging as the administered doses. If, by exception, an alternative pack is used, the effect on the shelf life must be considered.

There is a brief section on product release, covering the fact that there should be a two-stage release process:

- release of the bulk product prior to packaging; and
- release of the packaged product, including labelling.

This is called the 'technical green light' release.

There is also a brief section on free release, emphasizing the fact that analysis by other Member States after shipping of the products is not justified owing to the previously mentioned release process.

In the case of contract manufacture or contract analysis, the contract must make the nature of the material clear to both parties.

If any complaints are received, it is important that the results of the investigation are discussed between all parties – manufacturer, sponsor and investigator – in order to assess the implications for the trial itself, or any subsequent product development.

A recall procedure should be in place and should be fully understood by all parties.

Shipping, returns and destruction

The final section of the annex deals with three topics: shipping, returns and destruction. Shipping must be planned and organized by the sponsor. Following the 'technical green light' referred to previously, the sponsor is responsible for the final release of the product or the 'regulatory green light'. The packaging in which the product is shipped must be suitable to protect the product fully and receipt should be acknowledged. Transfers of clinical trials materials between different trial sites should only take place by exception and will often require the material to be returned to the manufacturing site, retested and relabelled before being transferred.

Any materials that are returned should be handled under carefully controlled conditions and should be stored in a segregated area. Destruction of materials should be carried out by, or at least under the instructions of the sponsor.

1.5 Drug registration in the European Union

In the early 1960s, a drug called thalidomide was prescribed as a sedative to pregnant women. As a result, there were thousands of babies who were born with limb deformities. This incident was the catalyst for the development of legislation to ensure that such a situation could not happen again. In order to prevent it, it was recognized that there was

a need for a mechanism to license all pharmaceuticals before they can be released on to the marketplace. From that point on, all products were required to have a marketing authorization.

The information provided in this section is a summary only. More information can be obtained from a booklet entitled *Pharmaceuticals in the European Union*, which can be accessed via the Pharmaceutical Unit website (see 'Websites' in Section 1.5.8).

1.5.1 Initial development of the framework

The first piece of legislation was Directive 65/65/EEC. This was followed ten years later by two further Directives (75/318/EEC and 75/319/EEC), which developed the concept of mutual recognition of marketing authorizations across Member States. The second of these two Directives set up the Committee for Proprietary Medicinal Products (CPMP), with the responsibility for ensuring that products complied with the original 1965 Directive.

Since 1975, the structure of the EU has been gradually developed and strengthened. The unit dealing with the regulation of pharmaceuticals is part of the Enterprise Directorate-General. It has three aims, which are as follows:

- to ensure a high level of protection of public health;
- to bring about a single market in pharmaceuticals; and
- to foster a stable and predictable environment for pharmaceutical innovation.

This unit has a number of areas of responsibility. Its duties under the heading of regulatory policy include drafting new legislation and ensuring that it is satisfactorily implemented. It facilitates the decision-making process of the Commission by drafting decisions and advising on procedure. It provides support to the pharmaceutical industry, with particular emphasis on innovation and competition.

The unit has a major role as a liaison with a number of external bodies. For example, it works within the International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. (There is a full explanation of the workings of the ICH in Chapter 11.) It also develops mutual recognition agreements with countries outside the EU. At a time when several Central and Eastern European countries are preparing for membership of the EU, it has a key role in helping these countries develop and upgrade their own pharmaceutical industries. Finally, the unit has an information technology (IT) role, which involves sharing of information between the individual regulatory authorities in the Member States and also ensuring transparency of information to the general public.

Other significant pieces of legislation included Directive 89/105/EEC, relating to regulation of prices, profits and re-imbursement, and Council Regulation EEC/1768/92, which permits the extension of a patent to compensate for the time lost during the marketing authorization process.

In 1995, a new system of authorization of pharmaceuticals was set up within the EU. This system provides two routes for obtaining a marketing authorization: the centralized procedure, and the mutual recognition procedure. In order to ensure that the new system would be able to operate effectively, it was necessary to establish a new agency.

1.5.2 European Agency for the Evaluation of Medicinal Products

The European Agency for the Evaluation of Medicinal Products, which is generally known as the European Medicines Evaluation Agency (EMEA), is responsible for evaluation of the safety, efficacy and quality of products that are submitted for a marketing authorization within the EU. The main responsibilities of the EMEA are as follows:

- to protect and promote public health by providing safe and effective medicines for human and veterinary use;
- to give patients quick access to innovative new therapy;
- to facilitate the free movement of pharmaceutical products throughout the EU;
- to improve information for patients and professionals on the correct use of medicinal products, to improve animal health; and
- to protect consumers of animal products and harmonize scientific requirements in order to optimize pharmaceutical research worldwide.

EMEA is a scientific body that advises individual Member States and other bodies within the EU, and uses a network of scientists from across the EU to facilitate the operation of the evaluation system. It has responsibility for the procedures to authorize pharmaceuticals, monitor them once in the marketplace and withdraw that authorization if there is evidence of a problem. EMEA also operates information sources and electronic communication in order to enhance the safe use of pharmaceuticals within the EU. The CPMP is one of the arms of the EMEA.

1.5.3 The centralized procedure

The centralized procedure is the compulsory route for the authorization of biotechnology-derived products. In addition, it is an optional route for the authorization of innovative or high-technology products. An authorization obtained via this route is valid within all countries within the EU.

In summary, an application via the centralized procedure is assessed by the CPMP, which recommends a decision, to be taken by the Commission. At the time that the application is submitted, a CPMP rapporteur is appointed who maintains the role of liaison between the company and the regulatory authorities, even after the marketing authorization is granted. There are time-limits for each stage of the application and the total time permitted is approximately 550 days, including 120 days for an appeal, if the CPMP produces an unfavourable opinion. In other words, a successful application via the centralized procedure can take up to 18 months to result in a marketing authorization.

Figure 1.1 shows the stages in the process and the associated timescales.

This procedure is proving to be a popular one. In the first four years of its existence, more than 120 pharmaceuticals were approved via this route.

1.5.4 The mutual recognition procedure

The mutual recognition procedure was made compulsory in 1998 for any product that is to be marketed in a Member State other than the one in which it was originally authorized.

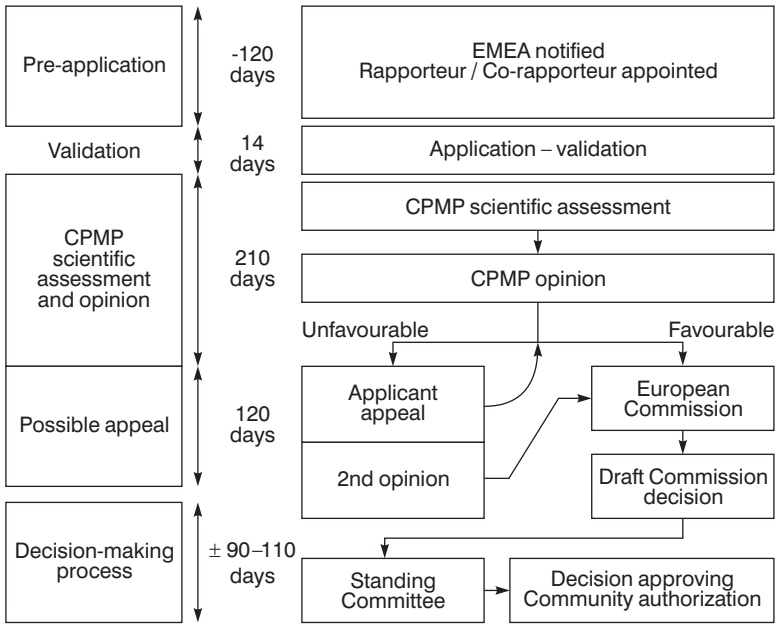

Figure 1.1 The centralized procedure.

A successful application is binding on all the Member States to which application has been made. It is also binding on further Member States once they receive a marketing authorization application for that product.

When the applications are made to more than one Member State at the same time, the first Member State to agree to evaluate the application becomes the reference Member State. Applications in the other (concerned) Member States are then suspended pending the outcome of the initial evaluation. Once the evaluation is completed, the report is forwarded to the concerned Member States before moving to the Commission for the decision-making process, which is similar at this point to the centralized procedure.

The timescale for the mutual recognition procedure is less than for the centralized procedure; however, it can still take up to 12 months for a successful application to be processed.

Figure 1.2 shows the stages in the process and the associated timescales.

1.5.5 Control of printed packaging materials

In 1992, a Directive (92/27/EEC) was issued relating to the information provided on printed packaging materials, specifically labelling and packaging leaflets. It defines the information that must be available on the outer packaging of a pharmaceutical for the benefit of the patient. The following information must be displayed on the label:

- product name
- pharmaceutical form and contents

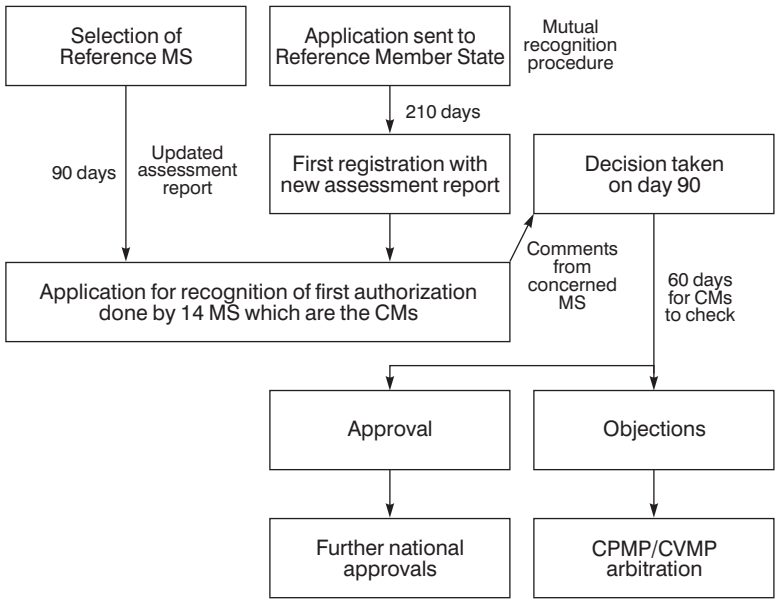

Figure 1.2 The mutual recognition procedure. MS, Member State; CMs, concerned Member State and see Abbreviations, page xv.

- name and address of marketing authorization holder
- authorization number and batch number
- composition, excipients and method of administration
- certain important warnings.

The packaging leaflet is required as well as the labelling. In addition to the above information, it carries a summary of the product characteristics and any contraindications.

Both the packaging leaflet and the label must be understandable to the patient as well as the doctor and/or pharmacist. The information must be printed in the language of the country in which it is being marketed. It is for this reason that many companies have national or regional packaging operations, even if they have a centralized factory for manufacturing the bulk product. In a tabletting operation, for example, where the finished pack is to be distributed across the EU, the product may be completely undifferentiated up to the point of compression, but the bulk tablets will then be packed into a variety of different packs, depending on the final destination.

1.5.6 Control of advertising

Also in 1992, Directive 92/28/EEC, which controls the advertising of pharmaceuticals across Member States, was issued. There are two types of advertising permitted. For products that are available over the counter (OTC), advertising is permitted to the general public and hence all the normal advertising channels are available. Examples of these are

the many advertisements seen on television for cough and cold remedies, particularly during the winter season.

For medicines that are only available on prescription, for those which have a psychotropic or narcotic content, where the product is eligible for reimbursement, or for certain specific therapeutic indications, advertising is only permitted to doctors and pharmacists. This is the reason why an advertisement for a novel anti-cancer treatment would not appear on television, but might be found in professional journals or in the advertising literature provided by medical representatives.

1.5.7 Pharmacovigilance

Purpose of pharmacovigilance

The surveillance of the safety of a medicinal product during the time that it is marketed is known as pharmacovigilance. Prior to granting of a marketing authorization, all pharmaceuticals go through the clinical trial stage, during which information is gathered regarding the effectiveness and safety of the product in use by humans. Sufficient information has to be gathered at this stage to ensure that the benefits of the drug are not outweighed by the adverse effects that it might cause. However, the information taken from the data during this stage is limited when compared to the amount of data that can be gathered once the product is released and is available to the entire population.

In most cases, the results of this wider source of data will be to reinforce the conclusions drawn as a result of the clinical studies and to confirm that the marketing authorization is valid. It is possible, however, that the balance of benefit and risk may change in the light of wider use, and systems must be in place to deal with that eventuality, including withdrawal of the marketing authorization, if appropriate.

Responsibility for pharmacovigilence

The responsibility for pharmacovigilance studies sits at a number of levels within the industry and regulatory bodies. At an industry level, companies are required to have pharmacovigilance systems set up, so that they can react to any problems identified.

There are three types of in-company studies that are carried out:

- individual adverse reaction case reports
- periodic safety update reports
- post-authorization safety studies.

In response to Directive 75/319/EEC and Council Regulation EEC/2309/93, each Member State has set up a national pharmacovigilance centre, which collates adverse reaction reports and has a system for taking appropriate action. These centres evaluate the reports from the individual companies, relating to nationally authorized products. For mutually recognized products, the reference Member State takes responsibility for evaluating the reports and communicating any required actions. Any issues relating to centrally authorized products are dealt with by the appropriate CPMP rapporteur.

Pharmacovigilance activities across the EU are co-ordinated by an EMEA Working Party that reports to the CPMP. At a global level, the World Health Organization (WHO) operates a Collaborating Centre for International Drug Monitoring, which deals with the national centres in the individual countries.

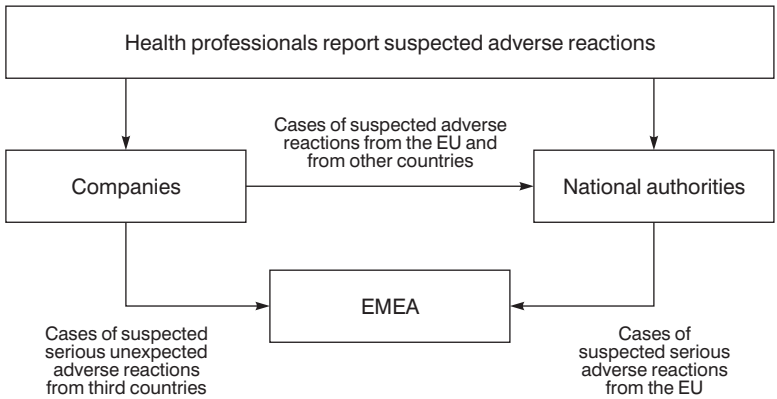

Figure 1.3 Pharmacovigilance: the reporting procedure for EU-approved medicines.

Under the marketing authorization system established in 1995 (see above), pharmacovigilance data are part of the marketing authorization dossier and have to be updated at the time of application to renew the authorization.

Figure 1.3 shows the interaction between the various bodies in the EU.

1.5.8 Channels of communication

There are a number of channels set up in order to facilitate communications between the regulatory bodies of the Member States, within the pharmaceutical industry and to the general public. These channels are called 'Eudra' projects and, wherever possible, they use electronic communication technology.

EudraNet

EudraNet stands for the European Union Drug Regulatory Network. It is a communication system for exchange of information between national regulatory authorities, EMEA and the European Commission. It is intended to extend this network in the future to authorities in the European Free Trade Association (EFTA) and Central and Eastern European countries (CEECs).

EudraTrack

This is a system that allows Member States to track the progress of marketing authorization applications within the mutual recognition system.

EudraWatch

This a system for management of pharmacovigilance reports that uses a standard format and content, as agreed within ICH, to allow easier communication between different regulatory bodies.

Eudralex

This is a very useful information source primarily for industry, but also for the general public. It contains legislation, guidelines, Notice to Applicants and other relevant documents, which can be downloaded directly via the internet. The following volumes (which can also be purchased in hard copy, bound format) were available at the start of 2002:

Volume 1 – Pharmaceutical legislation
Medicinal products for human use
Volume 2A – Notice to applicants
Medicinal products for human use
Procedures for marketing authorization
Volume 2B – Notice to applicants
Medicinal products for human use
Presentation and content of the dossier
Volume 3A – Guidelines
Medicinal products for human use
Quality and biotechnology
Volume 3B – Guidelines
Medicinal products for human use
Safety, environment and information
Volume 3C – Guidelines
Medicinal products for human use
Efficacy
Volume 4 – Pharmaceutical legislation
Medicinal products for human and veterinary use
Good manufacturing practices
Volume 5 – Pharmaceutical legislation
Veterinary medicinal products
Volume 6A – Notice to applicants
Veterinary medicinal products
Procedures for marketing authorization
Volume 6B – Notice to applicants
Veterinary medicinal products
Presentation and content of the dossier
Volume 7A – Guidelines
Veterinary medicinal products
General efficacy, environmental risk assessment
Volume 7B – Guidelines
Veterinary medicinal products
Immunologicals, quality
Volume 8 – Residue evaluation
Veterinary medicinal products
Notice to applicants for the establishment of maximum residue limits (MRLs) for residues of veterinary medicinal products in foodstuffs of animal origin
Volume 9 – Pharmacovigilance
Medicinal products for human and veterinary use.

This list will obviously become outdated with time. The appropriate website should be consulted to obtain information about later volumes.

Websites

There are a number of useful websites available, which can be used to access and download information.

The Pharmaceutical Unit website (http://pharmacos.eudra.org) provides information on registered products, Commission committees, draft legislation and policy documents.

Press releases, access to departments of the Commission and links to other institutions and agencies can be reached via the European Commission's EUROPA server (http://europa.eu.int).

There is an Official Journal of the European Communities, which contains the previous 20 days notices, EU treaties, current EU legislation and recent judgements of the Court of Justice. This journal can be found at (http://europa.eu.int/eur-lex).

1.6 Drug registration in the USA

In the USA, federal controls over the drug supply began with the inspection of imported drugs in 1848. In 1862, the Bureau of Chemistry was established within the Department of Agriculture. In 1927, the Bureau of Chemistry was reorganized into two separate entities: regulatory functions were located in the Food, Drug and Insecticide Administration, and non-regulatory research was located in the Bureau of Chemistry and Soils. In 1930, the latter organization was renamed and the FDA (Food and Drug Administration) was born. In 1940, it was transferred from the Department of Agriculture to the Federal Security Agency, which was converted in 1953 into the Department of Health, Education and Welfare. However, in 1968, the FDA was again moved, this time to the Public Health Service.

Finally, in 1988, the Food and Drug Administration Act established the FDA as an agency of the Department of Health and Human Services with a Commissioner of Food and Drugs appointed by the President with the advice and consent of the Senate. This Act also sets out the responsibilities of the Secretary and the Commissioner for research, enforcement, education and information.

During the time that the FDA was developing and establishing its roles and responsibilities, there was a similar development in the laws that control the manufacture and sale of pharmaceuticals in the USA.

1.6.1 Development of US drug laws

The original Food and Drugs Act was passed in the USA in 1906. However, it was completely revised 30 years later when it was found to be inadequate. The thalidomide incident in Europe in the 1960s was an echo of a similar tragedy that occurred in USA in the 1930s, which also precipitated a change in the way in which pharmaceuticals are controlled. A total of 107 people died as a result of taking Elixir Sulphanilamide, which

contained a poisonous ingredient. In 1938, the Food, Drug and Cosmetic Act laid on the companies the responsibility for proving the safety of a drug before it could be marketed in the USA. In addition, the concept of factory inspections was introduced.

In 1962, as a result of the thalidomide incident in Europe, the control of drugs within the USA was strengthened with the introduction of the Kefauver–Harris Drug Amendments. These required that, in addition to safety, the effectiveness of the drug must also be demonstrated. The requirement was retrospectively applied to all the drugs that had been registered since 1938. At the same time, the mechanism for adverse drug reaction reporting was set up.

Since the 1980s, there have been a number of other changes to the law, including the definition and management of 'orphan drugs' (Orphan Drug Act 1983), and measures to reduce the requirements for registration of generics, in terms of time and money involved (Drug Price Competition and Patent Term Restoration Act 1984).

In addition, there have been various changes in drug regulations, which have not involved a change in the law. These include measures to protect the rights of subjects within clinical trials (Protection of Human Subjects; Informed Consent; Standards for Institutional Review Boards 1981) and a move to short-circuit the process for obtaining new drugs for people with life-threatening diseases, by moving to approval after Phase II trials (Procedures for Subpart E Drugs 1988). Full details of the development of US drug laws can be found in a paper entitled 'The evolution of US Drug Law' on the FDA website (http://www.fda.gov/fdac/special/newdrug/benlaw.html).

1.6.2 Center for Drug Evaluation and Research (CDER)

The early years

The CDER began life as the Drug Laboratory, set up within the Bureau of Chemistry in 1902. The objectives of the laboratory were the standardization of pharmaceuticals and the unifying of analytical results. In 1908, the Drug Laboratory was reorganized for the first time. It was renamed the Drug Division, and subdivided into four laboratories: the Drug Inspection Laboratory; the Synthetic Products Laboratory; the Essential Oils Laboratory; and the Pharmacological Laboratory. Of these subdivisions, the Drug Inspection Laboratory became the main enforcement arm of the Drug Division.

Over the next ten years, the Division of Drugs added two new elements: the Pharmacognosy Laboratory was created in 1914 with the responsibility for investigating crude drug products and the reduction of waste during manufacture. In 1916, an office was established to investigate false and fraudulent labelling of drugs.

In 1923, the Office of Drug Control was set up as a replacement for the Division of Drugs. The Office was responsible for all pharmaceutical controls, including crude drugs, manufactured drug ingredients, drug preparations and patent medicines. Over the next few years, the Office expanded to include chemical, medical, veterinary and pharmacology units, together with a unit for special collaborative investigations.

In 1935, the Office of Drug Control was renamed the Drug Division. At the same time, the responsibilities for pharmacology were removed to a separate office, since there was an increasing need for pharmacological investigations in relation to adulteration of foodstuffs.

The Food Drug and Cosmetic Act of 1938

The Food Drug and Cosmetic Act of 1938 established the concept of the NDA (new drug application) by which all drugs had to be reviewed before they could be marketed. Within the first year, the Drug Division received over 1200 submissions.

In 1945, the Drug Division was renamed as the Division of Medicine. A major review of its activities in 1955 highlighted the fact that the review process needed to be speeded up and that, for this to happen, both manpower and budget should be significantly increased. In 1957, the Division became the Bureau of Medicine. During the same reorganization, the seven scientific divisions within the FDA were combined to form the Bureau of Biological and Physical Sciences. The Bureau of Medicine consisted of five branches with responsibility for new drugs, drugs and devices, veterinary medicine, medical antibiotics, and research and reference.

In 1961, the branch with responsibility for new drugs became a division in its own right. It contained five branches: the Investigational Drug Branch, which evaluated proposed clinical trials for compliance with investigational drug regulations; the Controls Evaluation Branch, which reviewed the manufacturing controls proposed by drugs makers; the Medical Evaluation Branch, which assessed safety and efficacy data in NDAs; the New Drug Status Branch, which consulted with manufacturers about their NDAs and proposed dosing schedules for new products; and the New Drug Surveillance Branch, which evaluated adverse reaction reports.

Over the next 20 years or so, the bodies with responsibility for the regulation of pharmaceuticals continued to evolve in response to changes in legislation and priorities. There was a further reorganization in 1965, another (encompassing much of the FDA) in 1969, and others in 1974, 1982, 1984 and 1986.

1980s–1990s

In 1987, the Center for Drugs and Biologics was divided into two separate entities: the Center for Drug Evaluation and Research, and the Center for Biologics Evaluation and Research (CBER). The main offices of the CDER were: Management; Compliance; Drug Standards; Drug Evaluation (I and II); Epidemiology and Biostatistics; Research Resources; Pilot Drug Evaluation; Generic Drugs; and Professional Development.

From 1995, CDER was once again reorganized. The Division of Oncology and Pulmonary Drug Products was split into two separate Divisions; and nine new Offices were established. Included in the new Offices were three additional Offices of Drug Evaluation, an Office of Training and Communication, the Office of Review Management, the Office of Pharmaceutical Science, the Office of New Drug Chemistry, the Office of Clinical Pharmacology and Biopharmaceutics, and the Office of Testing and Research.

CDER today

CDER is now the largest unit within the FDA. It is described on the FDA website as the ‘consumer watchdog in America’s healthcare system’. Its key responsibility is to ensure that only safe and effective drugs are allowed to reach the patient. The main areas of responsibility can be summarized as:

- Review of the new drug development process both during pre-clinical and clinical stages.

- Review of Investigational New Drugs (INDs) prior to granting permission for clinical trials.
- Review of new drug applications prior to granting marketing authorizations.
- Reviewing generic drugs by means of the abbreviated new drug application (ANDA), which concentrates on safety and bioequivalence, prior to granting marketing authorizations.
- Reviewing the safety and effectiveness of over the counter drugs prior to granting marketing authorizations.
- A number of post-approval review activities, such as post-marketing surveillance (see Section 1.5.7 for an explanation of pharmacovigilance); medication errors and advertising and labelling of prescription drugs.
- Miscellaneous areas of activity including orphan drugs, women's health issues, paediatric initiatives, environmental assessments and liaison with other parties within ICH.

1.6.3 The new drug application review process

Once a company has completed all the pre-clinical and clinical studies, the dossier is submitted for evaluation. All data are reviewed, including the adverse reactions that have been obtained, so that a benefit-to-risk assessment can be made. (It is accepted that no drug is without some risk, but that risk must be balanced against the potential benefits.)

As part of the review process, the key studies are identified and field inspections made of the investigators who carried out the studies to ensure the validity of the data.

In the past, the review time had averaged around 30 months. However, the FDA has been putting measures in place to reduce this and the current average is around 24 months. A system of prioritization has been devised, based on the nature of the drug. For example, any drug relating to the acquired immune deficiency syndrome (AIDS) is classed as high priority, as are drugs that offer a significant improvement in activity over alternative drugs already in the marketplace.

Within the FDA, there are a number of specific divisions that deal with different classes of drug. For example, the division of oncology and pulmonary drug products deals with all potential cancer treatments. All generic drugs are dealt with by the Office of Generic Drugs. In addition to the various divisions, the FDA has access to 17 standing advisory committees if they require a 'second opinion'.

1.7 Unlicensed medicines

Although the majority of medicines require a marketing authorization or product licence before they can be placed on the marketplace, there are some circumstances under which unlicensed medicines can be supplied. In the UK, such medicines are referred to as 'specials'.

Definition and use of 'specials'

'Specials' are unlicensed relevant medicinal products for humans, which are specially prepared by order of a doctor or a dentist for an individual patient. The control of the manufacture, distribution and supply of such products is covered in an MCA Guidance Note No. 14 'The supply of unlicensed relevant medicinal products for individual patients'. (The exemption does not apply to other unlicensed products such as herbal remedies and investigational medicinal products.)

'Specials' can only be provided for an individual patient who might have special needs that cannot be satisfied by the standard products available on the marketplace. For example, some patients may be allergic to a particular ingredient. Alternatively, some patients may be unable to tolerate the more usual dosage form; a patient with throat problems might be unable to swallow tablets or capsules, and could require the medicine to be dispensed as a liquid. Responsibility of prescribing such a product lies with the patient's doctor.

'Specials' may only be ordered by certain groups of people:

- doctors or dentists
- pharmacists in hospitals, health centres or pharmacies
- licensed wholesale dealers supplying to one of the above.

It is the responsibility of the party supplying the 'special' to ensure that the product is only for purposes as specified in the regulations. This includes checking on the professional status of the person buying the product and ensuring that they are aware of the unlicensed status of the drug.

Manufacture of 'specials'

'Specials' may only be manufactured by a company or organization holding a 'specials' licence, which is applied for in the same way as any other manufacturer's licence. The manufacturing facility will be subject to inspection by the regulatory authorities in the normal way.

There are major differences in the production of 'specials' as opposed to licensed pharmaceuticals. The batch size is very small, the preparation time is relatively short and the process is generally manual. Hence it is common for a number of different products to be in progress within different areas of the same room at the same time. This has particular implications for product security systems and cleaning procedures to prevent cross-contamination.

There is no requirement for QP release on a 'specials' order (see Chapter 8 for a discussion of the role of a qualified person); however, release should be carried out by an independent QC person and all records should be kept for a specified time period pending inspection or the need to review the audit trail.

Distribution of 'specials' can only be carried out by licensed wholesalers and full records must be kept. A supplier of 'specials' may advertise the service supplied, but not the individual products available.

Any medical practitioner who orders 'specials' is restricted in the amount of liquid and solid dosage forms that they may hold in stock. However, a pharmacist may hold stock of 'specials' in anticipation of an expected prescription.

There is an obligation, extending to all parts of the 'specials' supply chain, to keep appropriate records on sources and destination of each order. In addition, any adverse reactions must be notified to the regulatory authority.

1.8 Good manufacturing practice (GMP)

GMP is the concept that covers the assurance of the safety and effectiveness of pharmaceuticals during all the stages of manufacturing. It thus covers the identification of suppliers and purchase of all starting materials, both raw materials and packaging materials; the approval of those starting materials for use; and their use in the manufacture and packaging of finished pharmaceuticals. The requirements of GMP cover such topics as quality management, personnel, documentation, premises and equipment, materials handling, validation, contract manufacturing, and self-inspections.

GMP is discussed fully in Chapter 4 of this volume. No further discussion is appropriate at this point.

1.9 Good distribution practice (GDP)

GDP is the concept that covers the assurance of the safety and efficacy of pharmaceuticals from the time that they leave the factory gates to the point at which they are used by the patient. The requirements of GDP cover such topics as the establishment of a quality system, personnel, documentation, premises and equipment, deliveries to customers, returns of distributed product to the warehouse, self-inspections, and the information that must be provided to the appropriate authorities.

GDP is discussed in full in Chapter 5 of this volume. No further comment is made at this point.

2

Quality assurance and control

2.1 Introduction

Within the pharmaceutical manufacturing environment, the various functions related to quality management are critical. This chapter deals with two of the three main functions, quality assurance (QA) and quality control (QC). The third element, good manufacturing practice (GMP) is dealt with separately in Chapter 4.

This topic is potentially confusing because of the need to understand clearly the difference between quality management, QA and QC. Therefore, the chapter begins with a review of the interrelationship between the three. This is followed by a review of the definitions of each function and the differences between them. We then move on to cover the responsibilities of QA and QC in detail.

2.2 Relationship between quality management, QA, GMP and QC

The relationship between quality management, QA, GMP and QC can be viewed as a type of a cascade arrangement as shown in Figure 2.1.

Quality management, with the overall policy of the organization towards quality, comes above everything else. Next comes quality assurance, which is the unit that ensures the policy is achieved. GMP is a part of quality assurance; it deals with the risks that cannot be tested and builds quality into the product. Quality control is a part of GMP: the part that is focused on testing of the environment and facilities, as well as the testing of the materials, components and product in accordance with the standard.

The above relationship looks at quality management in the context of the pharmaceutical company that is manufacturing the product. However, we can also look at the relationships in a wider sense, in a global context and more from the point of view of

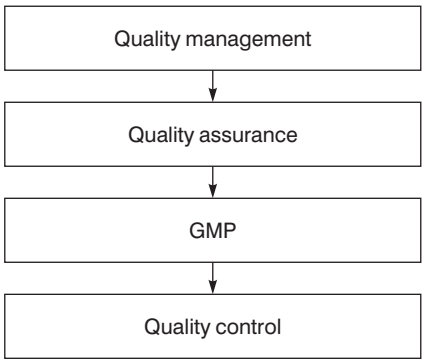

Figure 2.1 The relationship between quality management, QA, GMP and QC.

documentation. For this, we can use the image of an arrangement of glasses that is sometimes seen at more extravagant celebrations, where champagne is poured into the top glasses and gradually cascades down to the bottom.

Documentation cascade

At the top of the cascade are the international and national policies, codes of practice and standards, which govern everything that is done in the pharmaceutical industry. These overflow down into the next part of the cascade.

At the second level are the statements of the company goals, mission statement and values to which the company wishes to adhere. These should be designed to meet all the national and international codes that apply. They set the overall framework within which the company will operate. This should include references to public health and to the environment.

At the third level is the company quality policy that stems from the mission statement. This will be designed to deliver the mission statement, goals and values that the company has set for itself.

At the fourth level is the company quality system that is developed following the policy statement. This is designed to ensure that quality policy is achieved in reality and that it is not just fine words.

At the fifth level are the major departments' strategies involving R & D, manufacturing and QA; these set out how they will achieve their contribution to the quality system that has been developed. Here they should describe the major policies that they will implement to meet the requirements of the company quality system.

At the sixth level are the procedures and standards that have been developed in each department to implement the strategies. This is now taking the whole quality issue much more deeply into the working of each department.

At the base of the cascade are the individual job instructions and performance of the work to meet the standards and procedures that have been developed. It includes the critical records that are made of each part of the manufacturing process. In this way all the elements form a cascade that is closely linked. Each level provides a reference for the level below it. All the activities are closely aligned with one another and eventually to the achievement of the national and relevant international standards.

Having set the various functions within the overall context, the remainder of the chapter returns to the individual organization with specific reference to quality management, QA and QC.

2.3 Definition of quality management

Although the first chapter of the EU GMP guidelines is entitled 'Quality management', there is no definition of the term in this document. However, it is defined in the WHO GMP texts as 'the aspect of management functions that determines and implements the "quality policy" '. (Incidentally, this definition agrees with that contained in the international standard ISO 9000, which is discussed in detail in Chapter 3.)

The manufacturer is obliged to 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 the patient at risk because of inadequate safety, quality or efficacy.

The pharmaceutical product quality parameters are laid down in individual product specifications. These specifications ensure that the product fulfils the basic requirements of identity, purity, strength and bioavailability. They are described in detail in the marketing authorization or product licence.

- Identity: The product must comply with the information given on the product label.
- Strength/potency: The product contains the quantity of each ingredient claimed on its label, within the applicable limits of the specification (release and shelf life). This may be determined by chemical testing (strength) or by reference to a biological standard (potency).
- Purity: This is defined as the extent to which a raw material or a drug in dosage form is free from undesirable or adulterating chemical, biological, or physical entities as defined by the specification.
- Bioavailability/biopharmaceutical properties: Upon administration, the product must provide the active ingredient for the intended therapeutic/biological availability. Bioavailability is the rate and extent of absorption of a drug from a dosage form as determined by its concentration/time curve in the systematic circulation, or by its excretion in urine.

The commitment of the company to the general quality philosophy should be laid down in a document signed by management. This quality policy is a formal corporate statement by the senior managers of the company of its overall intentions and direction relating to quality. The senior managers of a company should be considered as the board of directors or the general manager of the company, and the plant or factory managers together with the senior managers responsible for production and quality control.

There are two basic elements to the function of quality management.

2.3.1 Quality system infrastructure

There must be an infrastructure in place that covers the organizational structure for quality management, sets up the procedures and processes that need to be carried out, and ensures

that appropriate resources are available to carry out those procedures and processes. A company needs to have a plan to develop all these items and a statement of its intent to carry out that plan. It is only when all the elements of this plan have been carried out that there is a system of quality management in place.

Any company or organization making pharmaceuticals should show that there is a structure, an organization dedicated to making the products correctly. This structure must have the backing of the most senior management of the company to be sure that it will succeed. (This topic is covered in more detail in Chapter 6.)

2.3.2 Systematic actions

Once the infrastructure is in place, it needs to be seen to be carrying out a set of systematic actions, which bring the quality policy to life. It is these actions that make up the function of QA.

2.4 Definition of quality assurance

In the EU guidelines, QA is defined as 'a wide-ranging concept which covers all matters which individually or collectively influence the quality of a product'.

Inside an organization, quality assurance provides a management tool. In contractual situations, quality assurance provides confidence for the customer (whether that is a pharmacist, doctor or patient) in the quality of the drug being supplied.

An important part of the systematic actions is the availability of a complete system of standard operating procedures. They describe all the actions that need to be taken in a standardized way. This means that everyone involved in pharmaceutical manufacturing has a book of procedures, which guides them in the way that they should do their job. It thus provides a standardized way of working.

Hence, although there is a specific department within the company called QA, the achievement of quality assurance is not the duty of this single organizational unit alone, but is the responsibility of all staff members who can influence product quality in any way.

One specific aspect of QA is encompassed in the term itself. It is the process that gives assurance that quality will be achieved. It is about putting things in place *in advance* so that everything goes according to plan and there are no problems with the quality of the final product. It is therefore about preventative measures. (The whole topic of preventative rather than appraisal activities is discussed in more detail in Chapter 7.)

2.5 Definition of quality control

Quality control is defined in the EU guidelines as:

> that part of GMP that is concerned with sampling, specifications, 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.

In the strictest sense of the words, QC is an historical process in which proof is obtained that the appropriate level of quality has been achieved. Of itself, QC can have no effect on the quality of the product. It is merely a measuring process.

The quality control process is therefore primarily confined to laboratory operations, testing and/or inspecting samples of raw materials, packaging materials, in-process materials and finished products. QC staff will also monitor aspects of the environment that have an effect on product quality. However, in many companies, the QC department also has responsibility for many of the areas that relate to quality assurance. For a fuller discussion of this, see Chapter 6.

2.6 Responsibilities of QA

Each of the various guidelines and codes of practice that are referred to in this book and are listed in the glossary cover QA in a similar way, although the specific details tend to vary slightly. This section commences with a review of the approach taken with the EU guidelines (and consequently within the PIC/S guidelines, see Chapter 11 for a full discussion of PIC/S). The same requirements are detailed in the WHO text. Specific differences within FDA documents are discussed later.

2.6.1 QA requirements within the EU, PIC/S and WHO

Product design and development

It is important to ensure that products are formulated and developed in accordance with QA principles. If all of the development work is carried out with a commitment to QA, it becomes easier to achieve QA in the rest of manufacturing. This implies compliance not only with GMP, but also with GLP requirements. (See Chapter 1 for a detailed discussion of quality requirements apart from manufacturing.)

Specification for production and control

Written specifications are essential for all aspects of manufacturing and supply. These specifications should state what must be achieved and how. They will cover all starting materials, intermediates and finished products, together with process specifications and analytical methodology.

Managerial responsibilities

There need to be a defined organizational structure and clear job descriptions for all personnel, particularly those in managerial positions. This is required to ensure that there are sufficient qualified and experienced people available who have the correct training to carry out their responsibilities. (This topic is covered in more detail in Chapter 6.)

Control of starting and packaging materials

This relates to management of purchasing, receipt, sampling and testing of raw materials and packaging materials. This is one of the key examples of quality being the responsibility of all functions within the organization. Purchasing personnel may not necessarily believe that they have anything to do with product quality. They may believe that they have much

more to do with the finance department. Indeed, they may actually report to finance. However, it is important that they only purchase materials from approved suppliers and according to approved specifications. Their performance objectives should under no circumstances be based purely on purchasing as lowest cost.

Control of intermediate materials

There is a requirement to ensure that all intermediate materials be controlled appropriately and for all in-process checks to be set up and carried out.

Control of finished products

Similarly, there is a requirement to ensure that all the necessary measures are in place for the manufacture and testing of finished products.

Batch release

Batch release can only be authorized by the qualified person after all the checks have been done to ensure that the product has been produced and controlled in accordance with the established specifications and the registered product details or other appropriate regulation. The registered product details will state what the standards are that the product must meet.

Control of storage and distribution

During product development, stability testing will have been done. The result from the stability testing is a set of specified conditions under which the product should be stored. Normally this will be a specification relating to temperature and humidity. However, additionally, there may be a specification for exposure to light and/or other parameters.

Arrangements should be in place throughout the storage and distribution chain that the product will not be exposed to conditions that could adversely affect the product. This means that all aspects of the distribution chain need to be covered from the factory through the wholesaler to the hospital, pharmacy or drug store. This is a difficult aspect for the manufacturer, since in many cases, the ownership of the product moves to another company once the product leaves the factory gates. This is very much an issue of influence rather than power or authority.

Self-inspection programme

A key part of the management of the manufacturing operation is the auditing of the operation for its compliance to all quality requirements. The auditing is done at several levels within the company, as discussed in Chapter 11. Self-inspection is the internal audit function existing within the departments.

Once all the above requirements have been addressed, a company can be said to be working within quality assurance principles.

2.6.2 QA requirements within the FDA

There is no reference to QA as a function within the 21 CFR Parts 210–211. However, the various requirements listed in Section 2.6.1 above are covered within 21 CFR Part 211, with the exception of product design and development and self-inspection programmes.

2.7 Responsibilities of QC

In the EU guidelines QC has its own section within the introductory paragraphs, outlining the requirements to be achieved in a satisfactory QC function. However, in addition, there is further material in a later chapter, which covers the requirements in more detail. A different approach is adopted in the FDA requirements, although in general the sentiments expressed are the same.

This section again begins with a review of the EU (and hence the PIC/S) documentation and then makes a comparison with the FDA.

2.7.1 QC requirements within the EU and PIC/S

Adequate resources

The QC department must have adequate resources to carry out its responsibilities. These resources come in a number of different forms. There must be: adequate laboratory facilities, either in house or by the use of government or contract laboratories; appropriately qualified, trained and experienced personnel; and finally, approved documented procedures covering all the operational duties of the department.

The operational tasks of the QC department are as follows: sampling; inspecting; analytical testing; monitoring of all materials and environmental conditions in the factory; releasing or rejecting materials for production use and finished products.

The objects of these activities can be taken from the following list: starting materials (both active ingredients and excipients); packaging materials (both primary and secondary materials); intermediates; bulk products; finished products; and environmental conditions.

Hence, in order to carry out a full audit of the level of QC resources within a company, it is possible to adopt a matrix approach, as shown in Table 2.1. By combining any one of the resources in the first column with any one of the tasks in the second column and any one of the objects in the third column, a checklist can be drawn up against which a gap analysis can be carried out.

Sampling

Sampling should be carried out according to methods approved by the QC department and only by approved personnel. It is not a requirement that all sampling is carried out by QA or QC personnel. Sampling of incoming materials is generally, but not always carried out

Table 2.1 Summary of quality control requirements

Resources	Tasks	Objects
Adequate facilities	Sampling	Starting materials
Trained personnel	Inspecting	Packaging materials
Approved procedures	Testing	Intermediates
	Monitoring	Bulk products
	Releasing/rejecting	Finished products
		Environmental conditions

by QC at the request of the warehouse personnel. In many companies, most in-process samples are taken by the production operatives. In some situations, such as in sterile areas or high-toxicity areas where access is restricted, sampling of finished products is also carried out by production personnel. The key point is not the department in which the sampler works, but that they have been trained in the appropriate methods by the QC staff.

Another important point is that all sampling should be done so that it is representative of the batch and that it is done in accordance with an SOP. However, if appropriate, QC personnel must have access to the factory to undertake sampling when necessary.

Validated or verified test methods

All test methods used within the laboratories and in-process control areas should be validated or verified. For a method that is taken from a recognized source, normally the national pharmacopoeia, it is sufficient to verify that the method can be carried out satisfactorily under the conditions existing within the company. However, if an analytical method has been developed in-house, it must be fully validated.

The topic of validation of test methods is fully covered in the ICH Guidelines Q2A and Q2B. Additionally, an overview of the subject is presented by Dr Mike Cope in the *European Journal of Parenteral Sciences*.

The validation of test methods includes consideration of accuracy, precision, linearity, repeatability, robustness and specificity. This means that the test methods should be challenged to demonstrate that they are able to give an accurate result on a repeatable basis. The method must be capable of being applied with precision. The results obtained must be linear over a range of acceptable responses. Finally, the results must be repeatable over a number of identical tests.

The actual parameters that are validated depend on the type of test being validated. Tests fall into a number of different types: identification tests; impurity/degradation tests, which may be quantitative or limit tests; and active assay/dissolution tests.

Adequate records

Records must be kept of all sampling, inspecting and testing of materials, intermediates, bulk and finished products. It is essential that records are kept of the work done by QC and during in-process testing. This is a key part of traceability, which must be achievable for all batches of product released on to the marketplace.

As batches are produced, it is important that all deviations from the normal manufacturing procedure are recorded or documented. Any impact on product quality must be assessed. It may be that additional product testing is required. Indeed, it may be that additional stability testing is found to be necessary.

Correct active ingredients and correctly labelled containers

QC must ensure that all the finished products contain active ingredients that comply with the qualitative and quantitative composition of the finished product described in the product registration dossier. It is most important that the materials used in manufacture comply with the details registered in the marketing authorization. It is on this basis that the product was developed and that all the stability testing has been done. All the clinical trials were also carried out using materials of a consistent specification.

It must be confirmed that the ingredients are of the required purity, since without starting materials of the specified quality, the company is unable to ensure that the rest of the process can be carried out with success. Although the requirement specifically refers to active ingredients, it is true to say that maintaining a consistent specification for excipients is also important for the quality of the final product.

The importance of using the proper containers must also be recognized. During development of the product, tests will have been carried out on the compatibility of the product with the container. Testing will also have been done to determine the effectiveness of the container in ensuring product stability. Use of non-compliant or non-approved containers will mean that the shelf life of the product cannot be guaranteed.

Labelling of finished product is very important. In some countries more than half of all product recalls are caused by incorrect printed components. These failures have a variety of causes. These range from mixing up the printed components during printing or labelling and packing to text errors in the printing that have not been detected. All such problems should be identified before the product is released, if QC is carried out correctly. (In fact, with an effective QA system, they should be prevented from occurring in the first place.)

Assessment of results

The results of inspection and testing of all materials must be assessed against the appropriate specification in order to confirm compliance. This assessment must also cover a full review of the process and packaging documentation. Any deviations must be fully investigated to confirm that they do not impact in any way on the finished product.

Product release

Release of batches of finished product should only occur after the authorized person has certified that production and quality control has been completed in accordance with the requirements of the registered product details.

Reference samples

Sufficient retained samples of the finished product in its final pack should be kept for one year past the expiry date. Additionally, retained samples of starting materials should be kept for two years after the date of release of the finished product, assuming the stability of the material can be maintained for this period of time. This is to allow for an evaluation of the product after it has gone on sale should there be a need. It will also allow ongoing stability trials to be carried out. These provide a security that the quality of the product is not gradually deteriorating over time.

2.7.2 Good control laboratory practice in the EU and PIC/S

The organization, management and key responsibilities of the QC department are covered in Chapter 6. At this point, it is sufficient to emphasize the fact that, under GMP requirements, the QC department must be independent from production in order to be able to carry out its responsibilities effectively.

Within the EU (and PIC/S) guidelines, there is a whole chapter on QC, which encompasses the way in which the department should operate. This can be termed as GCLP (good control laboratory practice).

Premises and equipment

There are no defined requirements for the premises in which QC laboratories are housed. It depends on what activities are to be carried out in a specific area. For example, the requirements for a microbiology laboratory carrying out sterility testing on finished products would be more stringent than for a microbiology laboratory carrying out microbiological analysis on raw materials for non-sterile products.

The key points are that the laboratories should be large enough to suit the level of production being monitored and to prevent cross-contamination between samples. (Since samples are never returned to production after analysis, there is no issue of reverse cross-contamination back to the manufacturing process.)

Laboratories should be located close to, but physically separated from, production areas. Particular care needs to be taken with laboratories that are used to analyse biological materials or antibiotics. It is also necessary to separate some types of analysis from each other. For examples, the antibiotic testing room should not be located close to the microbiology laboratory.

In physical or chemical laboratories, it is usual to separate out instrumentation, particularly equipment such as balances, which need to be protected from vibrations, from wet chemistry areas.

In many countries, particularly in developing industries where investment in equipment is low, a decision has been taken to contract out some or all of the QC activities. This is permissible, providing that the contract laboratory is audited and that all the GMP requirements of contracting are complied with. (This topic is covered fully in Chapter 4.)

Even in companies that have sufficient facilities to carry out their own QC functions under normal circumstances, it is common to contract out abnormal QC loads. For example, during the validation of a new facility, the environmental monitoring that is needed during the commissioning of the building and the additional sampling and testing required during the commissioning of the water treatment system will put a huge, short-term load on the microbiology department, which it might not be able to satisfy.

Documentation

In general terms, the treatment of documentation within the QC department is no different from that for the rest of the manufacturing environment. This topic is fully covered in Chapter 4. However, there are a number of specific points made with respect to QC documentation.

There are a number of key documents that are necessary for QC activities to be carried out satisfactorily. These are as follows:

- The specifications, which define the characteristics of the raw materials, packaging materials, intermediates and finished products.
- The sampling procedures for the raw materials, packaging materials, intermediates and finished products.
- The testing procedures and results of analysis of raw materials, intermediates and finished products (including all raw data).
- The analytical reports and/or certificates of analysis that were produced as a result of the tests.
- The raw data from environmental monitoring programmes, such as particle counts, settle plates and pressure differential readings.

- The data for the validation or verification of analytical methods, as appropriate.
- The methods and results of the calibration of laboratory instruments and other preventative maintenance activities.

Critical documentation, i.e. anything relating to a specific batch of product, must be archived for shelf life plus one year, together with the original data, such as laboratory notebooks and instrument printouts. Since the results will often be used in annual product reviews, consideration should be given to expressing the data in a form that allows for trend analysis. These days, data will frequently be transcribed into a laboratory information management system (LIMS) and hence these transcribed results can be used for the purposes of trend analysis.

Sampling

There must be a written procedure that covers a number of different aspects:

- How the sample is taken – from which part of the batch, using what equipment, how much is required and whether it should be kept as a single sample or subdivided.
- What the samples should be placed in – type of container and the information that needs to go on the label.
- Any special precautions – both in terms of protecting the material being sampled and protecting the person taking the samples.
- Storage conditions – both before analysis and afterwards if the sample is retained.
- Maintenance of sampling equipment – how it should be cleaned after use, where it should be stored and whether it needs to be recleaned prior to use.

Annex 8 guidelines

In addition to the paragraphs within the chapter on QC, there is an additional reference source specifically dedicated to sampling of starting (i.e. raw) materials and packaging materials. This is found as Annex 8 to the EU (and PIC/S) GMP guidelines.

The annex begins with a statement of the precautions to be taken with regard to training of personnel who will carry out sampling. (As previously stated, these may be personnel from QC, production or even, in some cases, warehousing.) The training should include the following areas of focus:

- The procedure for sampling – plans to determine how many samples should be taken, and how and with what equipment those samples should be taken.
- Cross-contamination issues – particularly in relation to sterile or toxic material
- Visual inspection prior to sampling – the state of containers, labelling details, etc., and the importance of recording unusual observation.

Sampling for identity testing

The next section deals with the sampling of starting materials and covers an aspect that, from experience, can cause confusion in some companies. The sampling rule of

$$\sqrt{n} + 1$$

where n is the number of containers, is often quoted during audits as the basis for a sampling plan for identity tests. However, according to Annex 8, the general rule is that all containers should be sampled and individually tested, since this is the only true way to

be sure that each container carries the contents that it should. Bearing in mind the large number of containers that may be involved in a delivery of materials such as starch or lactose, this can cause real logistical problems for companies, in addition to the workload in sampling and testing.

It is permissible to adopt a reduced sampling programme for identity testing providing that 'a validated procedure has been established to ensure that no single container of starting material will be incorrectly identified on its label'.

There are a number of areas to be focused on in achieving such validation. These would include: the nature of the supplier and the validity of their QA programme; the manufacturing conditions under which the material had been produced; and the nature of the material. For example, it is possible to consider that such reduced testing would be acceptable where the material is being purchased directly from the manufacturer and where the company is known to have a good understanding of GMP requirements and operates to this level of quality.

It is unlikely that such reduced testing would be acceptable where the material is being purchased through a broker. In this case, the original supplier may not be known and may change from delivery to delivery. Hence it would be impossible to gain sufficient assurance of the quality of manufacture to be certain that all containers would hold what the label claimed. Reduced testing should not be considered for materials that will be used in the manufacture of parenterals.

As a prerequisite for reduced sampling, there is an implication that the purchaser will have carried out audits on the supplier, including a visit to the manufacturing site.

Sampling for other purposes

For carrying out an analysis of the material to check its compliance with the material specification, it is permissible to sample a representative number of containers, and in some cases, to combine samples together. The method of sampling and the sampling plan may be defined in the pharmacopoeia or other national regulations. In any case, it should be the subject of a written procedure.

For packaging materials, it is also necessary to develop a sampling plan and to determine statistically how many samples should be taken. There will be a number of factors to be considered, including the source and nature of the material, together with the history of the supplier's performance and QA system.

Testing

There is a requirement that all the tests referred to in the marketing authorization should be carried out using the correct methodology, which must be validated or verified. All results should be checked to ensure that they are correct. The implication of this is that calculations and other data within laboratory notebooks should be checked and countersigned.

There is a statement of the minimum amount of information that should be recorded in the case of a set of test results. Whether the testing is carried out in the laboratory by a QC analyst or in the in-process control laboratory within the manufacturing area, by a production operative, it is important that the correct methodology, approved by QC, is used.

There should be a procedure for the preparation of such working materials as reagents, reference standards and culture media. This should include reference to the method of

preparation, the labelling requirements, expiry date conditions, storage conditions and records to be kept.

The whole topic of the use of animals for testing purposes is covered in GMP by a single paragraph that highlights the need for quarantine procedures, identification and records.

2.7.3 QC requirements within the FDA

The first mention of QC within 21 CFR Part 211 is in Subpart B, 'Organisation and Personnel', where the role of the QC unit is outlined. Responsibilities include testing and release of all raw materials, packaging materials, intermediates and finished products and reviewing of documentation associated with all aspects of manufacturing. These responsibilities cover not only the in-house manufacturer, but also the production carried out by contractors. The management of quality within USA is covered in more detail in Chapter 6.

QC is obviously a key factor throughout the FDA requirements. However, there are a number of subparts within 21 CFR 211 that relate specifically to QC activities.

Control of components and drug product containers and closures (Subpart E)

This section deals with the need for written procedures covering all aspects of control. There is a reference to the need for visual inspection on receipt and quarantining of deliveries pending testing and release. The sampling procedure is covered in some detail, as are the testing requirements. There are also references to stock rotation, retesting requirements and the handling of rejected materials.

Finally, there is a section relating specifically to drug product containers and closures (which are described elsewhere in this chapter as primary packaging components). This deals with such topics as compatibility of the materials with the drug, the integrity of closure systems and cleanliness requirements, including those for sterile products.

Sampling and testing of in-process materials and drug products (Subpart F)

Subpart F is entitled 'Production and Process Controls' and deals primarily with controls being carried out within manufacturing. Section 211.110 covers the in-process sampling and testing of intermediates. It specifically states that the responsibility for testing and release of materials sits with the QC unit.

Laboratory controls (Subpart I)

There are seven different sections under this Subpart of 21 CFR 211. Under general requirements, there is a reference to the writing and approval of control mechanisms such as specifications, sampling plans and test procedures, and a review of which controls need to be in place.

The section on testing and release for distribution covers the criteria that have to be achieved before a batch can be released and the circumstances under which an exception can be made. Testing should include microbiological analysis, if appropriate. The need for

a written procedure for both sampling and testing is emphasized. The action to be taken with products that fail to meet acceptance criteria is also discussed.

The next section deals with the requirement to establish a stability-testing programme, which must be described in writing. The circumstances under which accelerated stability studies may be used are reviewed. Requirements in relation to homeopathic drugs are also covered.

There is a section on special testing requirements: these cover drugs that are sterile or pyrogen-free, to demonstrate the absence of micro-organisms or pyrogens; ophthalmic ointments, to demonstrate the absence of foreign particles, or harsh or abrasive substances; and controlled-release dosage forms, to demonstrate the rate of release of the active ingredient.

The next section deals with the topic of reserve samples. There are separate requirements for reserve samples of active ingredients and for finished products. Under general conditions, both active materials and finished product samples must be kept for one year past the expiry date of the finished product. However, there are special conditions quoted for radioactive materials, where the storage requirements are between three and six months after the expiry date of the product. For certain OTC products, which have no expiry date, and for the active ingredients contained in them, samples must be kept for three years after distribution of the batch.

There is a brief statement on the use of animals in laboratories, emphasizing the need for good control and records. Finally, there is a section on the QC requirements in the case of a batch of general pharmaceuticals that might be contaminated with penicillin. If the test for penicillin is found to be positive, release of the batch is prohibited.

Records and reports (Subpart J)

Much of this Subpart deals with the requirements for record-keeping during manufacturing. However, Section 211.194 covers the specific topic of laboratory records. Records must include a number of items: details of the sample; test methodology; quantity of the sample used in each test; all raw data obtained during the tests; a record of the calculations carried out; results of the test and a comparison with the appropriate acceptance criteria; and signatures of the analyst, and the person who checked the records and calculations. Records must also be kept of any changes to the established methodology; of all standards and reagents; of calibration of test equipment and of all stability tests carried out.

3

Quality systems

3.1 Introduction

This chapter deals with the subject of quality systems. Such systems are generally related to internationally recognized standards. One major standard is reviewed in detail here. ISO 9000 is the series related to satisfaction of customer requirements. A second standard is also discussed briefly. ISO 14000 is the series related to management of the environment.

For ISO 9000, a review of the make-up of the standard is presented. Since this standard is currently in a transition phase, there is a review of both the 1994 series and the 2000 series. This is followed by a discussion of how each of the standards can be applied within the pharmaceutical industry. The chapter also includes a number of case studies to illustrate specific points.

3.2 ISO 9000 series

The purpose of this series of standards is to guarantee that a company has a system that ensures the delivery of a product/service in conformance with quality requirements and that the system is being operated effectively.

The ISO 9000 series of quality standards was first published in 1994. It was approved by CEN (Comité Européen de Normalisation) and thus replaced the former national standards of all the members countries: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the UK. In the UK, it superseded BS 5750 and the previous European standard was EN 29001: 1987.

In the past couple of years, the series has undergone a significant review and rewriting. The revised standards were published at the end of December 2000. At that point, companies that were already accredited to ISO 9000 were given a maximum grace period

of three years in which to upgrade to the new standard. On the basis of this grace period, both versions of the series are reviewed in this chapter.

Before starting to look at the standards in detail, it is worth considering the main elements of a quality system.

3.2.1 Elements of a quality system

There are four main elements to a quality system such as those as described below. These equate to the layers of documentation and are: the quality manual, the quality plans, the quality procedures, and the quality records.

The quality manual

This is the key document that describes the company's quality system in detail. It contains the statement of quality objectives, which should be signed by the managing director. It also describes how the company addresses each of the clauses within the standard, and identifies any that are not applicable. It makes reference to the quality procedures that relate to each aspect of the operation of the quality system.

This is a controlled document, which means that it has an approval signature, issue number and date. All changes are recorded in a change control register and only the latest version of the document should be in circulation.

The quality plans

These are the second-level documents that describe how a company's quality system is applied to a specific contract or project. They are operational by nature and, as such, are controlled documents, usually according to project requirements.

The quality procedures

These are the third-level documents that describe how various activities are carried out. They cover what has to be done, who is responsible, the frequency and, if appropriate, the location of the activities. Quality procedures cover both the operation of the quality system and the operational aspects of the company's business. (See the case study in Section 3.5 for an alternative approach to quality procedures.) Each procedure should cross-reference to the quality records that are produced as a result of the activity.

Once again, these are controlled documents, with the same requirements as those described for the quality manual above.

The quality records

Quality records are the fourth-level documents that are produced during the operation of the company. They cover both the operation of the quality system – minutes of management review meetings and reports of internal quality audits – and the normal activities of the company – batch-manufacturing records, training records, etc. As operational documents, these are not controlled in the same way as the manual or the procedures.

3.2.2 ISO 9000: 1994

The series consists of three main standards, related to a variety of products and/or services provided by the supplier in question.

- ISO 9001: *Quality systems – Model for quality assurance in design, development, production, installation and servicing* is appropriate for a supplier who provides all aspects of a business from the original design of the product/service through manufacturing and supply to servicing, according to contractual agreements. Servicing relates to an agreement to provide a service periodically, rather than one-off activities relating to repairs. For example, an instrument manufacturer that designs the equipment, manufactures and sells the units, and offers an annual recalibration service.
- ISO 9002: *Quality systems – Model for quality assurance in production, installation and servicing* is appropriate for a supplier who is involved in all aspects other than the original design of the product/service. For example, a company that produces pharmaceuticals under licence, which sells the products and deals with any customer complaints.
- ISO 9003: *Quality systems – Model for quality assurance in final inspection and test* is appropriate for a supplier who makes or supplies items from materials provided by a third party, carries out an inspection process, and then delivers and services a product/service, but has no involvement in the original design or production. For example, a contract medical device company that assembles the finished articles from components supplied by the patent holder, tests the finished product and has a contractual agreement to provide servicing to the patient.

In addition to the main standards listed above, there are a number of supplementary standards that provide help in application. These are listed in the bibliography. Of particular note are ISO 8402, which deals with terminology, and ISO 9000 Parts 1–3, which provides guidelines on how to apply the standards in practice.

ISO 9001

Since ISO 9001 is the most comprehensive of the three main standards, it is the one that is reviewed in detail below. Where there is a significant difference in relation to the other two, this is noted in the text.

The standard is made up of four paragraphs. Of these, the main one is paragraph four, which is divided into 20 clauses. A company is required to demonstrate that it has systems in place to address each of these clauses, in so far as they are applicable to the business of that company.

Whilst the standard was developed primarily for the control of quality of a physical product, it can be applied just as successfully to a service company. Most of the clauses apply in both cases; however, as indicated below, there are some that do not have any meaning in the context of a service.

In the following description of the standard, the company being accredited to the standard is referred to as ‘the supplier’, the company for whom the product or service is being provided is referred to as ‘the customer’, and the company that supplies product or service that goes into the final product or service is referred to as the ‘subcontractor’ (Figure 3.1). Hence this latter term applies equally to a source of starting materials for a

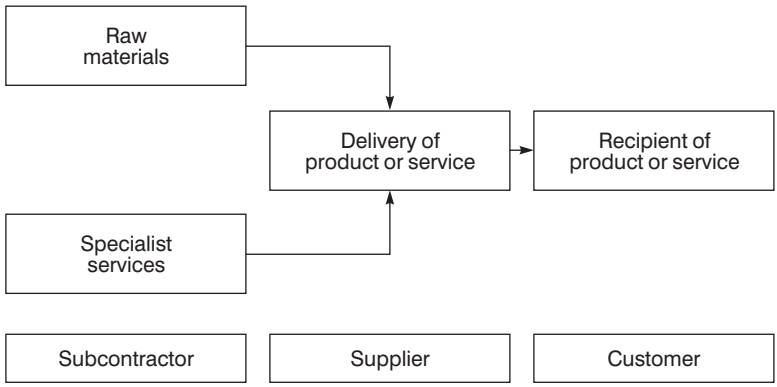

Figure 3.1 ISO 9001 terminology.

manufacturing operation, or to a source of labour or specialist services related to the final contract.

Clause 4.1 Management responsibility

There are three main requirements within this clause, relating to quality policy, organization and management review.

In terms of quality policy, the executive management of the company must define the quality policy and demonstrate its commitment to that policy. The policy will include specific objectives relating to quality and there is a requirement to ensure that these objectives are understood throughout the organization.

In terms of organization, there is a requirement to identify the responsibility of personnel in relation to quality and to ensure that individuals have the authority to carry through those responsibilities. In practice, this means as a minimum, having an organization chart and job descriptions in place, and ensuring that everyone understands the roles of each person within the company. It is also important to ensure that there are adequate resources available to maintain the quality of operations. There is a requirement that a management representative is appointed with responsibility for administering the quality system on behalf of the executive.

The management review requirement for the system is an ongoing review of all aspects to ensure their effectiveness. It involves, amongst other activities, a regular meeting held with members of the quality team to update them on any changes to the system and to check progress on specific actions.

Clause 4.2 Quality system

There are three main requirements covered by this clause. They are the general requirement to set up a quality system, and specific requirements relating to quality procedures and quality planning.

The general requirements detail the need for a system, which includes a quality manual, quality procedures and operational documentation – the quality records. These requirements are reviewed in more detail later in this chapter.

The quality procedures are required to document the system. There are actually two types of procedures required: those relating to the operation of the quality system and those relating to the activities of the company. In some cases, these are separated out, in order to prevent confusion. (See the case study in Section 3.5.)

The purpose of quality planning is to ensure that all measures are in place to allow the system to operate effectively. It may be a simple as referring to the appropriate procedure within each clause of the quality manual and cross-referencing these to the relevant quality record.

Clause 4.3 Contract review

This is the clause that deals with the process of winning a contract. It covers general requirements, review, amendments to a contract and keeping records.

The general requirement specifies that a system for management of contract review shall be in place. The review process is making sure that all requirements of both the customer and the supplier are clearly stated, that any differences between what has been requested and what is going to be supplied are resolved. It also requires a check that the supplier has all the necessary resources in place to carry out the contract.

No matter how carefully the review process is carried out, it is inevitable that in some contracts, the original requirements will be restated at a later date. It is important that a system is in place to ensure these amendments are recorded and accepted by both parties. Finally, full records of the contract review process must be kept as part of the quality records for the project.

Clause 4.4 Design control (applicable to ISO 9001 only)

This clause has nine sections relating to general requirements, design and development planning, organizational and technical interfaces, design input, design output, design review, design verification, design validation and design changes.

The general requirements merely state that there is a need for documented procedures to cover all aspects of the design process, as detailed in the following eight sections. (In fact, in all the following clauses, where there is a section entitled ‘general requirements’, it is merely a restatement of the purpose of the clause. To prevent repetition, these sections will not be discussed under the remainder of the clauses.)

Design and development planning involves the preparation of full plans for each design activity, which will be updated over time. It also involves identification of the appropriate personnel to carry out the activity.

Organizational and technical interfaces are a recognition of the fact that different parts of the company will have an input into the design activity. All necessary information flows are identified and set in place.

The design input requirements relate to the specific requirements of the customer and here there is a link back to the contract review process. They also take account of any regulatory requirements that need to be satisfied.

The design output stage is the point at which compliance to the stated requirements is demonstrated. Reference needs to be made to any acceptance criteria relating to the operation of the design and any factors that are critical to its correct operation.

Design review is a documented process by which all functions involved in the design have the opportunity to review, and comment on, progress. This process is extended into the design verification stage, during which the outputs are compared with the inputs, in

order to confirm that all requirements have been met. Prior to release of the design, a further stage, design validation, is carried out, in order to confirm that all the user requirements have been met.

Finally, there needs to be a formal system in place to ensure that all changes to the design are documented and approved prior to being carried out.

Clause 4.5 Document and data control

This clause relates to two separate types of documentation: that relating to the quality system itself (quality manual, procedures and records); and documents received from outside the company in the course of carrying out projects, such as drawings or specifications from customers. There is no distinction made between hard copy and electronic documents or data. The clause covers general requirements, document and data approval and issue, and document and data changes.

Document and data approval and issue requires that an appropriate person shall review and approve all controlled documentation. There must be a system in place to ensure that any obsolete documents are removed from the system and that only the current version of any document is in use at any time. Furthermore, the same authorized person should review all changes to documents and data, and keep a full history of all changes on record.

Clause 4.6 Purchasing

This clause relates to the control of purchasing in relation to materials, products or services that go towards delivering the final product or service to the customer. Hence it would include the purchase of raw materials in a manufacturing company or subcontractor services that are to be sold on. It would not cover ancillary purchases such as supplies for the company cafeteria.

The clause has four sections, dealing with general requirements, evaluation of subcontractors, purchasing data and verification of purchased product. Evaluation of subcontractors requires a system both for initial evaluation and selection, and also for control of the output of the subcontract over the period of the project. A list of approved subcontractors should be maintained.

Documentation recording purchasing data requires a detailed description of the product or service being purchased with reference to any specifications or applicable test methodology. All purchase orders must be reviewed to ensure that requirements are adequately defined prior to issue.

Verification of purchased product relates specifically to purchases that are verified at a subcontractor's premises. There are two methods of verification reviewed: where the company reviews the purchase themselves; or where the customer or their representative reviews the purchase.

Clause 4.7 Control of customer-supplied product

This is a short clause that deals with the situation where the customer supplies material of some kind that will be incorporated into the final product or service. It requires the setting up of a system to check the material on receipt, and to store and maintain it in appropriate conditions while awaiting its use.

In the context of a service organization, this clause will generally only refer to documentation. As such, it could be dealt with under Clause 4.5 Document and data control, in which case, this clause would be not applicable.

Clause 4.8 Product identification and traceability

This is another short clause covering the requirement to ensure full traceability of all materials from receipt through use to delivery and installation at the customer's premises. This traceability shall be documented and will be at the level of individual batches, if appropriate. The use of this clause is determined by production or contractual agreements.

Clause 4.9 Process control

This clause is one of the key areas of the entire standard and complements the control covered in Clause 4.4 (Design control). It relates to control of all the activities other than design that make up the product or service to the customer: production, installation and servicing. It requires documented procedures for carrying out all activities (referred to as operational procedures in the case study in Section 3.5), the use of appropriate equipment, monitoring of specific process parameters and the provision of suitably qualified personnel.

Clause 4.10 Inspection and testing

This clause is divided into five sections, covering general requirements, receiving inspection and testing, in-process inspection and testing, final inspection and testing, and inspection and test records.

Inspection and testing of received materials must normally be carried out before the materials can be used. In the event that an emergency requires use prior to verification, it is essential that there is full traceability to permit recall and replacement in case there is found to be any non-conformity. The level of inspection and testing that is carried out can vary, depending on the degree of assurance that is in place regarding the quality systems operated by the subcontractor.

There is a requirement for a system of in-process inspection and testing to be in place at appropriate stages during the contract. However, the main inspection and testing is carried out at the final stage, to confirm that the finished product or service complies with the customer's requirements. This stage should be completed in full, and the results authorized and signed off before the product or service is released to the customer.

Full records must be kept of all stages of inspection and testing. These records will include details of any failures against defined acceptance criteria and the subsequent actions that have been carried out.

In the context of a service organization, there is little or no inspection of materials. However, testing can be considered to cover a review of milestones during the progress of a project plan.

Clause 4.11 Control of inspection, measuring and test equipment

This clause is applicable to delivery of products rather than services. It deals with the monitoring and control of all equipment that is used to inspect or test the product to demonstrate that it complies with customer requirements. Such test equipment itself must be fully tested and calibrated against known national or international standards, and these calibration records must be available for inspection by the customer, if required. The clause contains two main sections: general requirements and control procedure.

Clause 4.12 Inspection and test status

Once again, this is a clause that relates to delivery of a product rather than a service. It requires that the status of the product (awaiting test, passed, failed) be clearly identifiable at all times, to ensure that only approved material or product be used or released to the customer.

Clause 4.13 Control of non-conforming product

This clause deals with the management of problems that are discovered. It consists of two sections, covering general requirements, and review and disposition of non-conforming product. The main intention of the clause is to ensure that product that fails to comply with customer requirements cannot be inadvertently used or released to the customer. It allows for investigation of the problem and rework, regrading or rejection. It also allows for use of product as it stands, if approved by the customer.

Although this clause relates specifically to product, it can be applied to services as well. Problems are identified and investigated, then solutions are determined and applied as appropriate.

Clause 4.14 Corrective and preventive action

This clause contains three sections, covering general requirements, corrective action and preventive action. It is applicable to both products and services. Corrective action is linked back to the previous clause, in that it is the company's response to a non-conformity. It deals with handling customer complaints, investigation of reasons for problems and implementation of the necessary actions to prevent recurrence.

Preventive action, on the other hand, is a quality assurance procedure that identifies potential problems before they occur and introduces controls to ensure that problems do not occur. In many cases, corrective action will result in the development of a complementary preventive action to ensure that the problem does not happen again.

Clause 4.15 Handling, storage, packaging, preservation and delivery

This clause is divided into six sections. Apart from the statement of general requirements, there is one short section covering each of the items listed in the title of the clause. Handling of materials must be carried out in such a way that no damage is caused. Storage under suitable conditions is required, including controls over receipt of materials into the stores and release of materials from the stores.

Protection of the product must be continued during packaging and delivery. Throughout the time that the product is under the control of the supplier, there is a requirement to ensure that it is preserved appropriately.

This clause is primarily applicable to companies that deliver a product. For a service company, the only physical product handled is generally documentation. This can be covered under this clause or under Clause 4.5 (Document and data control), whichever is more appropriate.

Clause 4.16 Control of quality records

This clause deals with the topic of maintenance of records and makes no distinction between hard copy and electronic records. It is necessary to store quality records for a specified length of time. The method of storage is chosen by the company, but the records

must be easily accessible in case they need to be reviewed. In some cases, such a review is the right of the customer or the customer's representative.

Clause 4.17 Internal quality audits

This clause relates to the requirement for a system to review the operation of the quality system to ensure its effectiveness. It requires the presence in the company of one or more trained auditors. In most companies, two auditors would be a minimum, since it is not acceptable for an auditor to carry out a review on an aspect of the system for which they have day-to-day responsibility.

Audit feedback is provided as part of the management review process and any non-conformity identified must have approved actions that are implemented within an agreed timescale.

Clause 4.18 Training

This clause requires that all personnel working on activities that may affect quality must be fully trained. This training may be by virtue of education, training or experience, or a combination of all three. The company is required to have systems in place to identify training requirements on a regular basis and to keep a record of that training once it has been carried out.

Clause 4.19 Servicing

This clause is specific to companies that are contracted to carry out servicing as part of the overall product or service. There is a requirement for a system to carry out, check and record all servicing activities. It should be emphasized here that in the context of this standard, servicing relates to a contractual agreement to carry out a regular service, such as calibration, rather than the definition of servicing related to one-off situations such as breakdowns.

Clause 4.20 Statistical techniques

This clause is made up of two sections, covering identification of need and procedures. It applies to companies where the use of statistical techniques forms part of controlling and confirming product quality. Procedures are required for implementation and control of such techniques.

3.2.3 ISO 9000: 2000

The publication of the new version of ISO 9000 series of standards represents a significant revamp and a fundamental shift in emphasis. The number of standards has also been reviewed and simplified. The series consists of three standards in total.

- ISO 9000: 2000 *Quality management systems – Fundamentals and vocabulary* replaces ISO 8402: 1994 and ISO 9000–1: 1994. It presents a comprehensive glossary and describes the background to the development of a quality system.
- ISO 9001: 2000 *Quality management systems – Requirements* replaces ISO 9001–9003 (1994 series) and presents in detail the requirements that a company has to comply with in order to obtain certification to the standard.

- ISO 9004: 2000 *Quality management systems – Guidelines for performance improvements* replaces ISO 9004 Parts 1–4, published between 1991 and 1994. It deals with continuous improvement in quality and is not intended as a standard to which companies will become accredited.

Differences from the previous standard

There are a number of significant differences between the new version and the old one. To start with, the language in which it is written is more straightforward. The layout of the document, with a full-page column of text, rather than the previous double column, makes for easier reading.

The terminology used for the three members of the supply chain has been amended to bring it into line with that used more commonly in organizations (Figure 3.2). The company providing materials, product or subcontracting services is now called 'the supplier' rather than 'the subcontractor'. The company to which the standard is being applied is now called 'the organization' rather than 'the supplier'. The term for and definition of the customer remains unchanged.

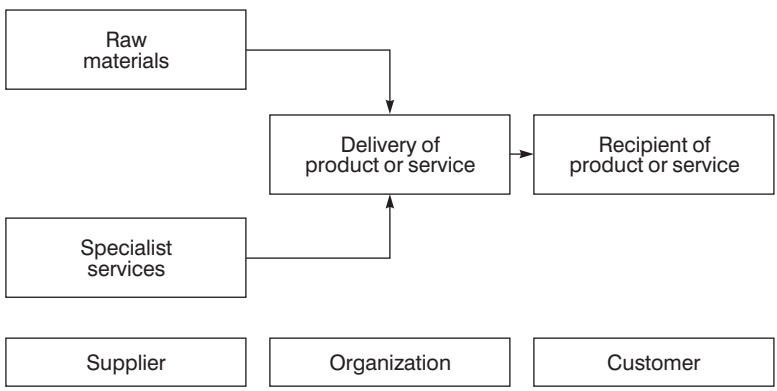

Figure 3.2 ISO 9000: 2000 terminology.

Key principles of quality management

The new standard is based on the following eight key 'principles of quality management'.

- Customer-focused organization: since organizations can only continue to exist if they have satisfied customers, there is a requirement to recognize customer requirements and to ensure that these requirements are at least met, if not exceeded.
- Leadership: this recognizes the importance of the leaders of the organization in identifying objectives, communicating those objectives throughout the company, and providing appropriate resources and environments to ensure that the objectives are achieved.
- Involvement of people: just as the leaders are important to the success of the organization, so are the remainder of the team. This requires provision of appropriate training and development, coupled with involvement and empowerment.

- Process approach: a process is defined as a system of activities that uses resources to transform inputs into outputs. The focus on processes requires that the activities of the organization are considered as a series of interconnected processes that can be managed together.
- System approach to management: this relates to the more effective management of an organization by viewing that organization as a series of interrelated horizontal processes, rather than a set of discrete vertical functions (often described as functional silos) as in the past.
- Continual improvement: this is seen as an ongoing objective of the organization. It is the point at which ISO 9000 and total quality management (TQM) really come together. (See Chapters 14–16 for a full discussion of TQM and other quality techniques.)
- Factual approach to decision making: this recognizes the need for data to be analysed and information taken into account when making decisions.
- Mutually beneficial supplier relationships: it is important for companies to develop a 'win–win situation' in their dealings with suppliers, since a partnership approach is beneficial for both parties.

For companies that are already accredited to ISO 9000, the transition to the new version should be relatively painless. The format of the quality manual may need to change, and there may be a need for fewer 'administrative' documentation systems, but the key operating and control procedures are likely to remain valid.

The 20 clauses in the 1994 version were a mixture of 'administrative' and operational controls, with no logical connection or order. In the new version, this has been amended so that there are four main headings, which together contain 21 subsections, as described below.

Management responsibility

The subsections within this part of the standard are: management commitment; customer focus; quality policy; planning; administration; and management review.

The senior management of the company must show that they are committed to the concept of the quality system, by ensuring that appropriate policies and objectives are in place, updated as necessary and understood by all members of the organization.

The focus of the company must be towards customer requirements, although regulatory and legal issues must also be dealt with.

Quality objectives must be quantifiable and relate back to the quality policy. They should be brought about by means of quality plans. These plans should consider processes, resources and continual improvement. They should be subject to a change control procedure.

The subsection on administration brings together a number of aspects that are scattered throughout the clauses of the 1994 standard. There is a need for responsibilities and authorities to be written down and understood by all members of the organization. The role of the management representative in particular is described. The need for a quality manual is reinforced and more detail is provided than in the previous version. The manual must cover the scope of the quality system, the processes that the company carries out and the procedures that are written to control those processes. The paragraphs dealing with control of documentation and control of quality records do not differ in content from those

in the 1994 version. The information on the management review process, however, is presented in more detail than previously.

Resource management

The subsections within this part of the standard are: provision of resources; human resources; facilities; and work environment.

It is the clear responsibility of the management of the organization to ensure that there are sufficient resources available to satisfy all customer requirements by successfully operating and, if appropriate, improving the quality system. In particular, personnel must be capable of carrying out their duties. This capability is developed by an appropriate mix of education, training and experience. The company must have training plans and records in place.

The organization has a responsibility for ensuring that the correct facilities are available, where facilities is defined in the widest sense as premises, equipment and support service. The facilities shall be maintained in such a way that an appropriate work environment is achieved, in relation to the product or service being produced.

Product and service realization

This is the part of the standard that deals with carrying out the operational tasks of the organization. In other words, it is the meat of the standard, relating to satisfaction of customers' requirements. The subsections in this part of the standard are: planning of the realization process; customer-related processes; design and/or development; purchasing; production and service operations; and control of measuring and monitoring devices.

Planning of the realization processes relates to the production for a specific project or contract. It is necessary first of all for the company to establish the objectives of the project. Secondly, they need to put in place the activities and records for carrying out the project. Thirdly, the appropriate resources are identified. Finally, quality assurance measures are set up.

The customer-related processes are covered next in the standard. These relate to the contract review process in the 1994 series of standards. The first stage is to identify all the customer requirements relating to a given project, plus any additional requirements identified by the company itself. Secondly, there is an internal review to ensure that the proposal or tender document produced for the project (including the quality plan) actually satisfies the previously identified requirements. Finally, there is a process put into place to facilitate communications with the customer in the event that any changes to the project need to be agreed.

The design and/or development process as described in the 2000 standard is very similar to the previous version, although some of the wording has been rearranged. The paragraph on organizational interfaces is combined with the one on planning, but otherwise, the process follows the same stages of planning, inputs and outputs, review, verification and validation.

The next part of the standard deals with purchasing. Essentially, as with design and development, there is no difference between this version and the previous one.

Production and service operations is a new subsection that brings together a number of topics that were spread around the 1994 standard. The first part deals with operations control, including ensuring that there is a product specification in place, together with

instructions for operators where required. There is also a requirement for appropriate equipment, monitoring and control instrumentation, processes for their use, and specific processes for the approval and delivery of product to the customer.

There is then a paragraph on identification and traceability, which equates to the equivalent part of the earlier standard. Similarly, there is a paragraph on customer property, which requires that any material supplied by the customer for use on the project is stored and handled appropriately.

The next paragraph, dealing with preservation of product, is a revised version of the earlier section on handling, storage, packaging, preservation and delivery. In the latest version, it is much shorter than previously, although the sentiment is still the same.

The final paragraph is one on validation of processes. In the original version of the standard, this was part of process control. In the later version, it is separated out. However, as before, the process of validation is referred to as an alternative to verification only. (See Section 3.2.5 below for a discussion of this in relation to pharmaceuticals.)

The final subsection of this part of the standard deals with control of measuring and monitoring devices. Whilst there is a much reduced quantity of text, the principle of the importance of calibration is carried through.

Measurement, analysis and improvement

The final part of the new standard brings together all the items that deal with verification that a project complies with requirements. The subsections in this part of the standard are: planning; measurement and monitoring; control of non-conformity; and analysis and improvement.

The subsection on planning emphasizes the need for the company to have processes in place to prove that a project at least complies with requirements and, if possible, exceeds them.

There are a number of aspects to measurement and monitoring. To start with, there is a requirement to set up methods for obtaining customer feedback on their satisfaction or otherwise, since this external focus is a key measure of the operational performance of the quality system.

The remainder of the paragraphs in this subsection deal with internal aspects of measuring the quality system. On a formal basis, there is the internal quality audit programme that covers all aspects of the system over a specified period of time (usually one year). On an individual project basis, there is a requirement to monitor not only the processes but also the outputs of those processes, whether product or service. This also covers the need for a formal procedure for product release prior to delivery to the customer.

The subsection on control of non-conformity is much shorter than the one in the original standard, but once again, the message is the same. Non-conforming product must be identified and controlled so that it is not delivered to the customer by accident. Where appropriate, such product should be reprocessed. If appropriate, the customer should be notified about the problems.

There then follows a new subsection on analysis of data. It was covered in the original standard under a couple of topics, but now has a subsection of its own. It requires that data collected about the quality system are analysed in order to determine how well the quality system is operating and where there is a potential for improvement. These data may be internal or external. This subsection relates back to the one on measurement and

monitoring, since the data collected under that subsection are turned into useful information in this one.

The final subsection of the entire standard covers the topic of improvement. It brings together the subjects of corrective action and preventive action, as described in the earlier version of the standard.

3.2.4 Comparison of ISO 9000: 1994 series and ISO 9000: 2000 series

For the many organizations that are already accredited to ISO 9000, there will be a need over the next couple of years to review their current quality system and decide what changes, if any, need to be made in preparation for changing to the new version. As a useful guide to this, the ISO 9001: 2000 document includes a set of very helpful tables, comparing the two versions.

3.2.5 Application of ISO 9000 standards to the pharmaceutical industry

The ISO 9000 standard is a generic one that can be applied to any industry. Many companies, particularly those in regions such as Eastern Europe and the former Soviet Union, where the industry is just emerging, consider using this route to achieve compliance to international pharmaceutical standards. The author is frequently asked what is the difference between ISO 9000 and GMP, and, on occasion, companies have stated that they have no need to work towards GMP because they were working towards ISO 9000 instead.

It is certainly true that there is a degree of similarity in the approach taken towards the two and, in fact, the latest version of GMP guidelines such as the EU and WHO guides both make reference to an ISO 9000-type quality system. However, the two are not completely equivalent. It is probably fair to say that any company that had in place all the systems required to comply with GMP would have little difficulty in obtaining ISO 9000 accreditation, at least in relation to its manufacturing operation. However, GMP has very little to say about the areas of sales and marketing. On the other hand, it is not necessarily the case that a company that has ISO 9000 accreditation would automatically be able to demonstrate compliance to GMP.

One aspect that particularly stands out as different between the two is validation. This is illustrated by reviewing Clause 4.9 (Process control) in the 1994 version of the standard. There is a requirement for the process of validation to be carried out by qualified personnel and for continuous monitoring to be carried out ‘where the results of processes cannot be fully verified by subsequent inspection and testing of the product’. This implies that inspection and testing is the preferred route to assurance of quality. However, in the pharmaceutical industry, the concept of quality assurance being of greater importance than quality control has long been established. (See also Chapter 7, for a discussion on the cost of quality.)

Clause 4.6 (Purchasing) in the 1994 version of the standard permits the possibility of purchased materials being used prior to their inspection and testing, in the case of an emergency. In the pharmaceutical industry, this should never happen. It is a requirement of GMP that all starting and packaging materials are inspected, tested and approved prior to their release for use within the factory.

Application of Clause 4.16 (Control of quality records) will tend to be industry specific. For example, in the pharmaceutical industry, records relating to manufacture of a batch of product must be maintained for one year longer than the expiry date of that batch.

There have been no guides written to date that discuss how to apply ISO 9000 standards in the pharmaceutical industry. However, there are guides produced by the Institute of Quality Assurance, Pharmaceutical Quality Group, covering ISO 9000 for suppliers to the pharmaceutical industry.

Tables 3.1 and 3.2 represent the author's view on the links between GMP and ISO 9000.

3.3 ISO 14000 series

The ISO 14000 series of standards deal with environmental aspects of management. ISO 14001 was issued in 1996 and requires a company to demonstrate that it has:

- an environmental management system, including an environmental policy;
- made an assessment of the impact of products or services and other activities on the environment;
- set up environmental objectives with quantifiable targets, and activities to achieve these objectives;
- set up systems for corrective action; and
- carried out a management review.

Once again, the system must be documented and must have appropriate monitoring and control programmes. Unlike ISO 9000, which is essentially a confidential system (apart from the relationship between the company and its assessors), the environmental policy produced by a company that is accredited to ISO 14001 must be available to the public. (Many companies would also make their quality policy available as part of their public relations exercise; however, it is not mandatory.)

In many countries, there is a growing concern about the environment and, increasingly, legislation is being put in place to ensure that companies do not act in a way that is detrimental to the environment. Hence there is even more of a drive for companies to achieve ISO 14001 than there is for accreditation to ISO 9000. Not only is it a good public relations tool, but in many cases, it is becoming a prerequisite for winning contracts. Some countries (such as the USA) are considering providing incentives to companies to encourage them to move in this direction.

The pharmaceutical industry uses large amounts of chemicals both in the primary synthesis of its actives and in the formulation of its finished products. The amount of waste material at these stages can be high. The amount of waste materials produced during packaging can also be high, particularly in a blistering operation. On this basis, the pharmaceutical industry is a prime candidate for ISO 14001.

Table 3.1 Comparison of GMP requirements and ISO 9000: 2000

GMP	ISO 9000: 2000
Quality management Principle Quality assurance Good manufacturing practice Quality control	Quality management system General requirements General documentation Management responsibility Quality policy Product realization Design and/or development
Personnel Principle General Key personnel Training Personnel hygiene	Management responsibility Management commitment Resource management Human resources
Premises and equipment Principle Premises General Production areas Storage areas Quality control areas Ancillary area Equipment	Resource management Facilities Work environment
Documentation Principle General Documents required Specifications Manufacturing formula Processing instructions Packaging instructions Batch processing records Batch packaging records Procedures and records	Quality management system General documentation
Production Principle General Prevention of cross-contamination Validation Starting materials Processing operations Packaging materials Packaging operations Finished products Rejects and returned materials	Product realization Planning of realization process Customer-related processes Purchasing Production/service operations
Quality control Principle General Good QC laboratory practice Documentation Sampling Testing	Product realization Control of measuring/monitoring Measurement, analysis and improvement Planning Measuring and monitoring Control of non-conformity Analysis of data Improvement
Contract manufacture and analysis Principle General The contact giver The contract acceptor The contract	Product realization Purchasing
Complaints and recalls Principle Complaints Recalls	Measurement, analysis and improvement Control of non-conformity
Self-inspection Principle	Measurement, analysis and improvement Improvement

Table 3.2 Comparison ISO 9000: 2000 and GMP requirements

ISO 9000: 2000	GMP
Quality management system General requirements General documentation	Quality management Principle Quality assurance Good manufacturing practice Quality control
Management responsibility Management commitment Customer focus Quality policy Planning Administration Management review	Personnel Principle General Key personnel Training Personnel hygiene
Resource management Provision of resources Human resources Facilities Work environment	Personnel Principle General Key personnel Training Personnel hygiene Premises and equipment Principle Premises General Production areas Storage areas Quality control areas Ancillary area Equipment
Product realization Planning of realization process Customer-related processes Design and/or development Purchasing Production/service operations Control of measuring/monitoring	Production Principle General Prevention of cross-contamination Validation Starting materials Processing operations Packaging materials Packaging operations Finished products Rejects and returned materials Quality control Principle General Good QC laboratory practice Documentation Sampling Testing Contract manufacture and analysis Principle General The contact giver The contract acceptor The contract
Measurement, analysis and improvement Planning Measuring and monitoring Control of non-conformity Analysis of data Improvement	Quality control Principle General Good QC laboratory practice Documentation Sampling Testing

3.4 Use of the quality systems approach within the pharmaceutical industry

As discussed above, the direct application of ISO 9000 within the pharmaceutical industry is a debatable issue. However, there is a move to adopt a quality systems approach within the industry in the USA.

3.4.1 Quality systems inspection technique (QSIT)

The QSIT programme was developed in the medical devices industry in the late 1990s. There was recognition by the FDA that their resources were constrained and that it was not possible to carry out full audits of all the companies within the required timescales. Hence the approach of inspecting subsystems was introduced.

The approach is based on a 'top-down' review of various elements of a company's quality system in order to determine the overall state of compliance. It is in contrast to the traditional 'bottom-up' review where specific problems are identified and used to evaluate the company's responses.

The first step in the QSIT approach is to carry out an overview of the subsystem to determine whether documented procedures are in place to satisfy requirements. This is then followed by an in-depth review of a sample of records to ensure that the procedures have been effectively implemented.

By reviewing key elements of the quality system, it is possible to evaluate whether the whole quality system in under control.

3.4.2 Drug manufacturing inspections (pilot program)

During the first half of 2001, the FDA established a pilot programme where the QSIT approach was applied to the manufacture of drug manufacturing facilities. Six key subsystems were identified, based on the key Sub-parts of 21 CFR 211. The results of this pilot programme are currently being evaluated. It would seem likely that this approach will become the norm for all inspections by the FDA in the near future.

3.5 Case study

A small, but rapidly growing, management consultancy, consisting of only seven staff, decided to apply for accreditation to ISO 9001. The original objective was to attain a recognized quality standard that could be used in tendering for local authority projects. However, it was quickly found that the major benefit for the company was in the setting up of internal systems that permitted the office manager to monitor progress on all outstanding projects. At any one time, there could be up to 50 projects on the books, at some point between quotation and project close.

Owing to the size of the company and the lack of excess resources, it was imperative that the bureaucracy in the system was kept to a minimum. Additionally, it was important that the system was simple enough to gain understanding and commitment from the fee

earners who were out on the road most of the time. It was, therefore, decided that the procedures that would be needed for the system should be split into two categories.

Firstly, there would be the quality procedures, relating to such activities as internal quality audits and management review meetings. These procedures would be primarily the responsibility of the management representative and the quality auditor. The remainder of the team would need to be aware of their existence and would be involved in the activities as appropriate, but would not have to know the procedures in full.

Secondly, there would be the operational procedures, which referred to the activities required to carry out the business of the company. These would include carrying out a contract review, management of projects and purchasing. These were the 'bread and butter' activities of the company, and these few documents would be fully understood and used by all members of the team.

The overall result was that the company gained its accreditation, the system was set up and operated effectively, but the amount of additional documentation seen and used by most of the team was minimized.

4

Good manufacturing practice

4.1 Introduction

Good manufacturing practice is the phrase that is used to encompass all the requirements that need to be complied with in the manufacture of pharmaceuticals that are both safe and effective. It is thus a very wide-ranging concept. As seen in Chapter 2, it is part of the concept of quality assurance.

Good manufacturing practice is generally abbreviated to GMP in Europe and many other parts of the world. In the experience of the author, the term GMP has entered a number of other languages in its original, untranslated form. In the USA, the phrase used is 'current good manufacturing practices', abbreviated to cGMPs.

The concept of GMP is also recognized in other industries, in particular the food industry.

In this chapter, there is a review of the definition of GMP and a history of its development in different parts of the world. A comparison is made between the various versions of GMP codes and guidelines in existence today. This is followed by a review of the basic requirements of GMP and how they are applied in pharmaceutical factories around the world. The chapter closes with a discussion of why there are often no 'right answers' in questions of GMP and the need for interpretation of guidelines by individual practitioners.

4.2 Definition of GMP

GMP is generally defined as 'that part of QA, 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' (European GMP guidelines; WHO guidelines).

From this definition, there are a number of points that should be emphasized:

- GMP is part of QA. In other words, it is a preventative operation that is designed to make sure things happen in the correct manner. This means that, unlike QC, the quality of any operation can be affected by the GMP measures that are put in place.
- There is a requirement for consistency. It is no good producing a batch of product correctly one day, if there is no guarantee that the same result cannot be obtained every day.
- GMP relates specifically to the manufacturing aspects of a product pipeline. This is defined as the point from which starting materials are purchased from approved suppliers to the point where finished product leaves the factory. Indeed, there is also a responsibility to ensure the quality of the product during distribution, even though at this point it is often outside the control of the manufacturer.
- Quality standards should be appropriate to the intended use of the product. Hence the requirements to be fulfilled for the manufacture of an aseptically filled injection will be far more stringent than those for the manufacture of a multivitamin tablet.
- The standards are previously defined in the application for marketing authorization. Hence there is a clearly defined process by which each product must be manufactured.

In a more simplistic definition, GMP can be described as the process of preventing cross-contamination and mix-ups. The difference between these is as follows:

- Cross-contamination occurs when different materials or products become mixed, either in large quantities or as trace amounts. The latter will occur particularly if cleaning procedures or separation systems are not effective.
- Mix-ups occur when different printed packaging materials, particularly labels, are mixed together.

There is one final consideration when looking at the definition of GMP. The term is actually used in two different ways. It is firstly, and most correctly, used as the part of QA relating to manufacturing. As such, there are detailed lists of requirements to be fulfilled, as described later in this chapter. Secondly, it is used in the generic sense to describe everything relating to the quality of pharmaceuticals. Hence, the various guidelines on GMP, discussed below, include sections on quality management and QA.

4.3 Different versions of GMP

There are many different versions of GMP in use around the world. As more and more countries improve the standards achieved within their pharmaceutical industries, they all go through the stage of wanting to have their own guidelines in place. Some of these newer variants are described later in this section. There are, however, a small number of versions in place that were developed some 30 years ago, when the concept of quality manufacture was being put in place. These versions will be discussed initially.

Firstly, however, the point should be emphasized that, although the wording of the various versions of GMP may differ to a greater or lesser extent, the spirit of what is to be achieved is the same in all cases. It is often a question of degree and interpretation.

4.3.1 GMP in an EU Member State: the UK

The first GMP guide to be produced in the UK was published in 1971. It was subsequently updated in 1977 (when the concept of good distribution practice for wholesalers was introduced) and again in 1983. From the late 1980s, the guidelines of the European Community (EC) were published and the national document was superseded (as were similar documents in other Member States.)

The familiar volume, known in the UK and many other parts of the world as 'The Orange Guide' after the colour of the cover, continues to be published in the UK. Its correct title is *Rules and Guidance for Pharmaceutical Manufacturers and Distributors*, and the latest edition was issued in 1997. It contains a number of documents relating to manufacturing licences and qualified persons in addition to GMP guidelines. However, the latter is a straight reproduction of the European text.

4.3.2 GMP in the European Union

The principles of GMP within the EU are laid down in Directive 91/356/EEC. As a result of this directive, all Member States were required to be in compliance by 1 January 1992. The directive covers all medicinal products sold in the EU, including products imported from elsewhere and products manufactured in EU for sale elsewhere. Until 2001, the application of the guidelines to the manufacture of clinical trials material depended on national legislation. However, as described in Chapter 1, the introduction of the Clinical Trials Directive has changed this situation.

The directive goes on to enumerate the main topics that are covered within GMP. These topics form a framework that has been adopted within other guides around the world. They are listed here in full, and will be referred to in later parts of this chapter.

- Quality management: there is a requirement for companies to have a QA system involving all personnel, both management and workforce.
- Personnel: this section deals with the requirements for sufficient personnel with appropriate qualifications and experience to carry out the duties that they have been assigned. It also covers the topics of training and personnel hygiene.
- Premises and equipment: companies must ensure that they have suitable facilities for the operations that are carried out in them. Due attention must be paid to design and construction, cleaning, maintenance and validation.
- Documentation: there are a variety of documents that are mandatory for companies to have in place when carrying out pharmaceutical manufacturing. These include specifications for all starting materials, packaging materials, bulk product, intermediates and finished products. Specifications are the documents defining the material and describing analytical tests, test parameters and acceptance criteria. Also required are the manufacturing formulae and packaging instructions, which are the master documents from which individual batch documents are derived; batch processing records and batch packaging records, which must be completed during the manufacture and packaging, respectively, of each individual batch of product; and standard operating procedures, which describe all activities that are not product-specific (such as operation of a piece of machinery or sanitation programmes for the various parts of a factory). This section also deals with the management of electronic data.

- Production: this section deals with general principles not covered in other parts of the directive, and also with validation and handling of all materials throughout the process.
- Quality control: although QC is covered briefly in the section on quality management, it is dealt with in much more detail in its own right in this section, which refers to personnel, facilities and activities of the QC department.
- Work contracted out: there are many reasons why companies might wish to contract out some of their manufacturing or analysis. For example, their facilities for producing a particular type of product might require refurbishment and it might be more cost-effective to contract out to someone else. Alternatively, they might not have a microbiology laboratory of their own and hence this part of the analytical requirements would be contracted out. Topics covered include the responsibilities of both parties to the contract and the contents of the document itself.
- Complaints and product recall: there is a requirement for companies to have in place tested procedures for the effective handling of complaints and product recalls. A complaint is generally received in relation to a single dosage unit or a small quantity of product that has been found to be defective in some way by the final customer or someone earlier in the chain. Management of the complaint involves investigation and appropriate reaction to the complainant. A product recall, by contrast, deals with the entire batch of product and involves removal of all units from the marketplace, pending investigation of a potential or actual risk to the patient.
- Self-inspection: part of the QA system for a company must include a formal system for self-inspection, including generation of reports and implementation of recommendations.

Each of the above sections forms a complete chapter in the GMP guidelines. In addition, there are specific annexes published on the manufacture of sterile medicinal products; biological medicinal products; radiopharmaceuticals; veterinary medicinal products; medicinal gases; herbal medicinal products; liquids, creams and ointments; pressurized metered dose aerosol preparations; investigational medicinal products; and products derived from human blood or plasma. Additionally, there are annexes on sampling of starting and packaging materials; computerized systems; and the use of ionizing radiation in the manufacture of medicinal products.

The number of annexes in the EU guidelines is growing all the time. The latest additions deal with validation, QP release of batches, parametric release and GMP for active pharmaceutical ingredients (APIs).

4.3.3 GMP and the USA

The GMP requirements related to pharmaceuticals manufactured and/or sold in the USA are embodied in the Code of Federal Regulations, title 21, Parts 210–226. Of these, the most important for mainstream manufacturing are Parts 210 and 211. Part 210 is a relatively short section, covering the status of GMP regulations, the applicability of GMP regulations and a set of definitions.

Part 211 is much longer and covers a wide range of topics under a number of subparts, each of which is broken down into a number of sections.

- Subpart A deals with general provisions, such as scope and definitions.
- Subpart B covers organization and personnel. It deals with roles and responsibilities.
- Subpart C is the part that deals with buildings and facilities, in terms of design, construction and maintenance.
- Subpart D discusses equipment requirements. Once again, it covers design, construction and maintenance. It also deals with specific topics such as automatic equipment and filters.
- Subpart E deals with the control of components and drug product containers and closures. It reviews their handling throughout the manufacturing process from receipt to use and emphasizes the fact that primary packaging components should be treated no differently from other starting materials.
- Subpart F covers production and process controls. It deals with such topics as reconciliation and in-process controls and testing.
- Subpart G is the part that covers packaging and labelling control. It reviews the requirements for the issue and use of labels and other packaging materials.
- Subpart H reviews the aspects of manufacturing that relate to holding (storage) and distribution.
- Subpart I covers the topic of laboratory controls.
- Subpart J deals with all aspects of records and reports.
- Subpart K covers the areas of returned and salvaged drug products.

4.3.4 GMP in Australia

The Australian Code of Good Manufacturing Practice was first published in 1969, primarily as an instrument to be used by inspectors involved in the licensing of pharmaceutical factories. It was revised three times over the following 20 years, before the latest version was published in 1990. It is obviously used not only by inspectors, but also by practitioners in deciding what is needed in order to comply with GMP requirements.

The Australian Code is published in two parts, with a number of additional annexes. The first part deals with the general provisions of GMP and covers all the usual topics, in a fair amount of detail. Additionally, there is a section on the use of computers. The second part deals with the manufacture of sterile products. In addition, there are appendices on the following topics: radiation sterilization; supplementary notes for hospital pharmacists; guidelines on tests for stability; guidelines on laboratory instrumentation; guidelines on industrial ethylene oxide sterilization of therapeutic goods; and guidelines for the estimation of microbial count in process water.

4.3.5 GMP and the World Health Organization

The WHO is a United Nations agency with responsibility for international health matters and public health. The approach of the WHO to GMP is that there is a need for a

'comprehensive approach to quality assurance, which, while retaining adequate rigour, had to be adaptable to the needs and economic circumstances of developing countries' (WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second Report, 1992).

In other words, the WHO guidelines are the basic minimum standard that should be attained by any country that is locally manufacturing pharmaceuticals. A number of countries in Africa and the Commonwealth of Independent States (CIS) have adapted this standard as their national one. The WHO guidelines on GMP are the technical reference source that underpins the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce and should be read in the context of this scheme. (For more details on the Certification Scheme, see Chapter 11.) However, in practice it is only applicable to countries that do not intend to export their products widely. In many countries, it is not accepted as an appropriate standard for imports. Increasingly, there is reference to the EU or FDA requirements in this context.

The first version of the WHO GMP arose from the WHO Health Assembly in 1967. It was published in 1968 and subsequently revised in 1971 and 1975. There were no further revisions until the latest version, which was published in 1992. The guidelines, along with many other useful reference texts, appear in the reports of the Expert Committee on Specifications for Pharmaceutical Preparations. In this case, the Thirty-second Report is the relevant one.

The latest version recognizes the existence of a number of major national and international reference texts to GMP. Additionally, it acknowledges the role of the ISO 9000 series of standards in the management of quality. (For a discussion on this series of standards, see Chapter 3.)

The layout of the WHO guidelines differs from that of the European and other national standards, although as already stated, the overall spirit of the guidelines is the same. It is published in three parts.

Part One covers the general approach to quality assurance and the main elements of a GMP system. Although in a different order to the EU guidelines, and with some subsections expanded into sections in their own right, the same topics are reviewed. Part Two reviews the separate responsibilities for personnel within production and QC in order to comply with the requirements of GMP. Part Three contains the annexes or supplementary guidelines. At the time of publication, there were only two: manufacturing of sterile pharmaceutical products, and good manufacturing practices for active pharmaceutical ingredients (bulk drug substances). It is intended that further annexes would be added with time.

4.3.6 GMP in the Arab World

A number of countries in the Middle East have their own GMP guidelines. However, in 1991, a guideline was published by the Arab manufacturers' union. The second and latest edition was published in 1995. It follows the model of the WHO guidelines described above. However, in the introduction, it is stated that it conforms to the international requirements of the WHO, EU and Japan (via ICH).

4.4 Comparison of different GMP guidelines

When working within a company, whether as a full-time employee or as a contractor on a project, there will always be one main reference document in use, depending on the country in which the company is located. However, different guidelines deal with some topics in differing degrees of depth and it is often useful to consult a number of source documents in order to clarify certain aspects.

4.5 Responsibilities under GMP

In the foregoing parts of this chapter, GMP has been discussed in the context of its wider sense. In other words, we have reviewed the major GMP texts in use around the world. However, as mentioned at the start of the chapter, the more specific meaning of GMP is the part of QA that relates to the manufacture of pharmaceuticals. In this section, this definition of GMP is examined in more detail.

The responsibilities that are laid upon a manufacturer of pharmaceutical products under the auspices of GMP are detailed in Chapter 1 of the EU guidelines on quality management. These responsibilities relate both to the function of production and QC. There are ten elements in total, and these are described as follows.

- Defined processes: all manufacturing processes should be clearly defined during development and reviewed on an ongoing basis to ensure that they are appropriate and capable of consistently producing the required result.
- Validated processes: all critical steps within a manufacturing process should be validated when the product/process is first introduced and whenever there are any substantive changes made to that process. This ensures that the process not only performs consistently but also can be proved, with documented evidence, to do so.
- Necessary facilities: it is important that all the appropriate facilities are in place. In this context, facilities is defined in its widest sense as trained, qualified personnel; sufficient, suitable premises; appropriate equipment and services; materials, correctly labelled in appropriate containers; standard operating procedures, and other documentation such as batch manufacturing records and batch packaging records; and appropriate arrangements for storage and transport.
- Clear documentation: manufacturing instructions and standards operating procedures should be clearly written in a manner that will be understood by the personnel for whom they are intended. They must be tailored to the specific facility in question.
- Trained operators: even with defined processes and clear documentation, manufacturing will not be carried out satisfactorily unless the operators are properly trained in all the necessary procedures.
- Appropriate records: all activities taking place during the manufacturing must be adequately recorded – if it is not written down, it did not happen. This documentation may be completed manually, or by electrical or electronic recording devices. In many companies, there is a mixture of both. However, in either case, there must be an effective control system for obtaining and maintaining these records. All process deviations must also be recorded and fully investigated before a batch can be released.

- Batch traceability: it is important that all manufacturing records are maintained in a suitable format so that full traceability is available. This particularly includes distribution records, which are critical in the case of a batch recall.
- Quality maintained during distribution: the responsibility for maintenance of quality does not end at the factory gate. It is important that throughout the distribution chain, appropriate controls and storage conditions are maintained. This is reasonably easy when the manufacturer controls the distribution channel. However, even when the products are distributed by other entities (such as wholesalers), there is still a responsibility to ensure that they are aware of and understand the importance of all such requirements.
- Recall system: whilst no company wants to have to deal with a recall situation, it is necessary for all companies to be prepared for this eventuality. A procedure must be in place, which has been tested in a 'dry run' to ensure that it will operate effectively.
- Complaints system: all complaints must be investigated to determine whether they are justified or not. If they are justified, it is necessary to determine whether this is a one-off occurrence or part of a trend. Actions must be put in place to rectify any immediate problems and prevent any recurrence.

4.6 Rules versus guidelines

The requirements of GMP are generally set out as guidelines, rather than rules. In fact, many of the reference documents have the word guidelines in their titles. GMP guidelines tell a company *what* is required. They rarely tell the company *how* that requirement is to be achieved. In other words, in the world of GMP, there are no right answers, only interpretations.

Having said that, there are often preferred solutions, which have developed through custom and practice within the industry. However, if a company chooses to adopt a different solution for a particular requirement, they are at liberty to do so. They have to prove to their government inspector, or other auditing body, that the approach they have taken is appropriate and scientifically proven to achieve the required result.

This reliance on personal interpretation of guidelines, rather than adherence to rigid rules, is an approach that is particularly difficult for some of the companies in the former Soviet countries to work to. The USSR had a wide range of standards in place that laid down the rules for construction of factories and manufacturing of products. Many of these standards are still in place and, on occasion, can conflict with the accepted custom and practice of GMP around the world. On the other hand, the lack of clear statements on what is allowed can result in confusion both amongst companies and licensing authorities. (See the case studies in Sections 4.8.1 and 4.8.2.)

4.7 Application of GMP

The earlier parts of this chapter have reviewed the guidelines that are produced in different countries to help companies achieve GMP compliance. The responsibilities under GMP were also discussed. The ways of application of some specific aspects of GMP are covered in great detail in other chapters. This section deals with the topics that do not fit neatly

elsewhere in the volume. The section is based on the nine chapters of GMP as presented in the EU guidelines.

4.7.1 Quality management

This topic is fully covered in Chapters 2 and 6.

4.7.2 Personnel

Within the pharmaceutical industry, people can be a source of great strength but also need a lot of attention. To make an investment in facilities and equipment merely requires money. However, in order to operate those facilities, it is necessary to have correctly educated, trained, motivated people working in the factory or laboratory. People's motivation can change and their behaviour may be modified due to circumstances beyond the control of management. Hence it is necessary to provide training to overcome their inherent weaknesses and build on their great strengths.

In managing personnel, a company needs to have in place a number of key principles that must all work in harmony, if GMP is to be achieved. The establishment and maintenance of a satisfactory system of GMP relies upon people: the people who develop the system, the people who use the system, and the people who examine the system to see if it has worked. People are involved, no matter how automated the process or how capital intensive the operation.

There must be sufficient people employed to carry out the work for which the manufacturer is responsible. These people must have the level of training and experience that will enable them to do their work.

Recruitment

One of the key factors in determining whether a company has the right personnel is the recruitment process that it uses. It is most important that the people that are recruited are selected from a group that can meet the particular requirements relating to the pharmaceutical industry. For example, all production operatives must be able to read, in order to be able to use SOPs and complete process records.

During recruitment, a medical examination should be included, to make sure that the individual does not constitute a risk to the products with which they will be working. Conversely, there is a responsibility on the company to ensure that the personnel are not put at risk by the products or processes. Operators working with cytotoxic products may need blood tests on recruitment and at six-monthly intervals thereafter. Operators who will work on visual inspection processes should also undertake an eye test on recruitment, with regular check-ups on a periodic basis afterwards.

Having sufficient people implies that some excess is needed to provide cover if required, such as for holidays and sickness. This can be a very difficult area and one that can be a much more demanding requirement for smaller companies than is perhaps the case for a multinational company factory or similar.

The duties placed upon any one individual should not be so extensive that they cannot cope, resulting in a risk to quality of the product.

Responsibilities

There should be a written organization chart and a clear job description for each member of the organization. These will help the company to see whether there are any training gaps that need filling or whether there are any areas of conflict, owing to too many people being trained in one area. The organization chart should make clear the independence of QA/QC from production.

It is important that all personnel have authority to carry out their responsibilities. This is very easy to say and sometimes not so easy to do. Problems can arise here in every size of company, from small private companies to very large multinational enterprises, owing to a combination of human interactions, and the pressures placed on people by the business considerations that exist in every company.

Personnel policies should be designed to encourage people to support the development and maintenance of very high quality standards in all the work that is done. Access to production, storage or laboratory areas should be restricted to personnel who have been properly trained to work in those areas. It is pointless to invest in recruiting and training good people, if they are then given the message that it was all a waste of time. This can happen, for example, if people from other parts of the company walk through the factory to reach the warehouse to pick up or deliver paperwork. All access to other areas of the company should be organized so that no entry to production, storage or laboratory areas is required.

Training

All personnel involved with materials and products should receive GMP training. This training should commence upon recruitment and continue throughout employment. The training should be appropriate to their needs and position within the company.

It is important therefore, that companies should have a written training programme, to ensure that all personnel understand the rules of behaviour that apply to them. As soon as someone is recruited, they need to understand what is expected of them and the risks to patients if the products they make do not conform to requirements. This initial training must be given to all employees who have a direct impact on product quality.

The training programme will tend to fall into at least two parts. The first part will be a general programme that all employees should receive, which explains the importance of GMP to the company. There may well be a second programme, explaining the specific issues about the individual's department.

There should be a written re-training programme for *all* employees to ensure that their skills are continually brought up to date and that they are introduced to changes in practice as these develop.

Training records

As employees go through their training, records should be kept of the training received and performance against tests. People have to realize that good performance is necessary otherwise retraining will be required. Training records must be kept so that, as employees move around the company, they are not required to carry out work for which they have not been trained.

People who work in some specific areas should receive additional training in relation to the nature of their work. Those people who work in sterile areas, with highly active or

toxic materials or sensitizing agents, should receive specific instruction in the special nature and hazards associated with these activities.

During training, every encouragement should be given to employees to discuss all aspects of quality and GMP fully with their trainers and amongst themselves. Encouragement should be given for staff to contribute to increased quality and GMP.

Visitors

One of the issues that needs to be addressed is how companies handle visitors. Essentially, they should be treated as risks to the product, and measures must be put in place to ensure that they cannot cause any hazard to product quality. Ideally, the company will do this by factory design, which means that visitors cannot access the factory areas in operation. This is usually difficult and so, if a visit is unavoidable, it is important that a full briefing is carried out in advance, full protective clothing is provided and strict instructions are given concerning where visitors may go.

Visitors to the factory are important. Factory visits can be a useful selling tool for the company. Additionally, there will be occasions when regulatory inspectors need access to the premises. However there must be no exception to the rules that visitors must wear the appropriate clothing to protect the product.

Hygiene

The last issue to be covered in terms of personnel is that of hygiene. It has already been mentioned that the recruitment process for direct operators in particular should include a medical examination. This should be repeated on a regular basis during the employment period. The definition of 'regular' will depend on the activities being undertaken and the products being processed.

Induction training for new operators should include basic training in personal hygiene and should state the level of hygiene that is required for working in manufacturing areas. There should be written procedures covering the need to wash hands before entering a manufacturing area. In addition, signs should be posted in the changing rooms to reinforce this.

If operators have an illness or open lesions that are likely to present a risk to the product, these individuals should not be allowed to carry out operations that involve handling of starting materials, intermediates and finished products until such time as the condition has cleared up. Since such conditions are not always going to be obvious to other people, operators must be trained to recognize such risks themselves and report them to the appropriate supervisor or manager.

Direct contact between the operator and the product should be avoided wherever possible. If it is inevitable, then gloves should be worn and, if appropriate, these should be disinfected after being put on.

Clothing

The type of clothing required and the changing procedure will vary with the activities being carried out. Used clothing must be stored in separate closed containers whilst waiting for cleaning.

The laundering of clean-area clothing must be carried out according to a written procedure and in an appropriate facility. If necessary, there should also be a procedure for sterilizing and storing clothing for use in the sterile area.

Smoking, eating and drinking should not be allowed in any manufacturing area, including laboratories and storage rooms. Chewing of gum should also be banned. There should be no plants kept inside any factory areas.

Rest and refreshment areas should be separate from manufacturing areas. Toilets should not open directly into production or storage areas; however, there should be a reasonable access procedure.

4.7.3 Premises and equipment

Location

The word premises refers to the buildings and land where manufacture of the products will take place. The land and buildings must contribute towards achievement of GMP by reduced risks of contamination, effective cleaning, preventative maintenance and minimized build-up of dirt and dust.

The first issue to consider is one of location. It is essential to recognize the impact that location can have on the premises. The geography of the area can affect the design of facilities. For example, is the location subject to earthquakes or regular flooding? What precautions need to be taken regarding continuity of supply of services?

The climate of the area is also important. If a company is handling gelatin capsules, then humidity can be of great concern. Perhaps it would be better to locate on the side of a hill above the plains to ensure reduced humidity.

Neighbours

It is necessary to consider any near neighbours from two different viewpoints. If the processing plant generates a lot of noise, it may be necessary to install soundproofing. If the plant is located near a residential area, there will be concerns from neighbours about safety issues, particularly in relation to waste products and possible spillages. (This is likely to be more of an issue for established facilities, since companies are less likely to obtain approval to build new facilities near residential areas these days.) Whatever the location, companies are required to take measures that prevent them polluting the surrounding area with product or by-products from the manufacturing processes.

Whilst the above points are as much to do with good neighbourliness as anything else, the question of what the neighbours do, and the effect that this can have on the pharmaceutical facility is very definitely a GMP issue. For example, if the premises are located next door to a steel mill or a stone mason, then the ventilation system will need to be designed to handle any dust generated.

Finally, thought needs to be given to what sorts of services are required and what is the standard of supply. For example, if electricity from the public service is subject to frequent breakdown, then there needs to be an alternative supply, particularly if the company is operating sterile areas.

Inside the premises: general points

There are a number of general points to be considered with regard to the inside of the premises. To start with, the design should make sanitation easier. Surfaces should be

smooth and should not be damaged by the cleaning methods and materials that are going to be used. All joints should be sealed and the ceiling/wall and wall/floor joints should be coved to provide a smooth surface between the two flat surfaces.

Premises need to be maintained if they are to continue to provide the environment for which they were designed. Hence, initial design should take into consideration the ease of maintenance. Many facilities are now designed with a service corridor at the rear or side of every manufacturing area. Wherever possible, all equipment, particularly moving and maintainable parts, is located against this service corridor. This enables the mechanics to undertake their maintenance without entering the manufacturing area.

All cleaning and disinfection of areas should be done in accordance with a written procedure. All these procedures should be designed and operated to ensure that cross-contamination and contamination are eliminated.

The services required at the factory must be able to be maintained at the level of quality required for production. As mentioned earlier, if a sterile area is to be operated but the electricity supply is very unreliable, then the permanent use of an auxiliary generator may be essential. Lighting, temperature, humidity and ventilation control systems should all be designed and operated to ensure that product quality is safeguarded.

Finally, the premises need to be designed and operated to prevent the ingress of insects and animals. Birds are often found to be the most persistent pest. Care must be taken that rodent and pest control measures are not a threat to product quality.

Ancillary areas

There are a number of ancillary areas that need to be provided, apart from the specialist areas that are discussed later in this section. Rest and refreshment rooms must be located apart from the areas used for manufacturing, packaging, storage or quality control. The type of activity going on will determine the degree of segregation. If only drinks are to be consumed, then provision of a separate room should be sufficient. If smoking and eating are to be allowed, then the segregation will need to be more extensive. The fumes from cooking and smoking must not be permitted to encroach on the production areas. This implies that special ventilation systems may be required for the kitchens and the cafeteria.

Facilities will also be needed for operators and all visitors to change their clothes and footwear. Storage will be needed for outdoor clothing. This will be particularly important in countries where extremes of weather are experienced in the winter. A system is also needed to ensure correct entry to the manufacturing areas. Many companies are now designing the entry to manufacturing areas as a one-way system with double-sided lockers. This means that all personnel entering a manufacturing area must pass through the change procedure in one direction. People exit the factory and gain access to their outdoor clothes from the other side of the locker. This prevents any possibility of cross-contamination.

Toilet and other wash facilities must not be directly accessible from manufacturing, storage or quality control areas. Hand washing facilities must be provided and their use encouraged. Consideration will need to be given to the provision of toilet paper, soap, towels or other types of hand-drying facilities.

Maintenance workshops should be separated from production areas. If tools are to be kept in a manufacturing area, then they should be kept in a container or cupboard specific for that purpose.

Flow design

When designing any facility it is most important to set out the principles upon which that design will be based. It is also important to ensure that the flows of process, material and people are brought together without conflict.

In considering process flow, the key issue is the sequence of events that will take place during the manufacturing process. For people working within the industry, this will be a relatively simple concept. However, the design may be produced by engineers and/or architects who are not familiar with pharmaceutical manufacturing. It is important to ensure that they are fully briefed in advance. Room data sheets are useful in this context to help describe the way in which the process is operated, the equipment that will be used and the services that will be required. These sheets can also be used to describe the environment that will be required by the product.

Material flow relates to the routing of different materials through the facility at different times during processing. This will include not only raw materials, packaging materials, intermediates and finished products, but waste streams as well. The status of the materials (whether they are quarantined, approved or rejected) should also be considered. Frequently this is done by marking the layout drawings with different coloured lines for each material type and with different thicknesses to show frequency of movement. In this way it is possible to identify areas of high movement frequency and where the floor is going to have to be very strong to resist the high workload that is placed on it. Materials should flow in the direction of manufacturing. There should be no cross-flow of materials.

The people flow deals with the routes that people will take when they enter the facility, when they move around from one department to another and when they leave. It is also important to consider how visitors will enter and where they will go.

Receipt and dispatch areas

Goods inwards and dispatch areas can be quite neglected areas of a manufacturing facility. However, they are actually the first point of entry of materials into the factory and the last point at which the company may have control over the products before they enter the distribution chain.

The design must ensure protection from the weather. If deliveries are to be made by tanker, there must be a means for making a clean transfer between the tanker and the storage tank. If a company is expecting deliveries or shipments by truck, then they may need to provide suitable facilities for the drivers to rest and also toilet facilities.

If incoming goods containers are stored outside before use, facilities may be needed to clean them before they can be opened for sampling, and before they are transferred into the warehouse.

A separate sampling area will generally be required. Sampling is the first stage in pharmaceutical processing, since the material will inevitably be exposed to the atmosphere. The sampling procedures used must prevent cross-contamination.

Warehousing

Separate areas must be provided in warehouse areas for materials of different status (quarantined, approved and rejected). This separation can be physical or electronic but, in the latter case, must be validated to ensure that it is secure.

Separate areas would also be required if a company is storing hazardous materials including flammables or narcotics. These requirements would tend to be covered by national legislation.

All storage requirements with respect to temperature and humidity control must be catered for. This implies that both monitoring and control should be in place. Examples of materials that may need special controls are vaccines and gelatin capsules. Depending on the expected volume of such materials, it is common to control conditions in small parts of the premises, rather than the whole warehouse.

Dispensary

Many companies use dispensaries to weigh out all the materials for the different manufacturing lines, rather than providing balances in each production area. The dispensary is hence an area that has a high number of materials moving through it during the day, all of which will be exposed to the atmosphere at some point.

The design, operation, control systems, recording and cleaning of the dispensary must all ensure that there is no risk of cross-contamination. Sufficient space must be available for storage of bulk containers, dispensing, order collation and order storage, whilst maintaining ease of movement and separation between orders.

Manufacturing areas

One of the biggest issues facing many companies around the world is that of segregation of certain processes. This is essential, particularly for sensitizing substances such as penicillins and cephalosporins, toxic or highly potent materials, or some hormones. In some cases the reason is the potentially damaging or fatal effect on sensitive patients. In other cases it is to protect the operators from the product. In all cases where these special precautions are needed, the design must take into consideration all movements of services, as well as materials and people. Design of air-handling systems should take into account the prevailing wind; inlets should not be located close to outlets.

Corridors and walkways should be wide enough to accommodate all personnel, and all material movements that are likely to occur. Corridors should not be used for storage.

A pharmaceutical manufacturing facility uses a number of services including compressed gases, water, vacuum, electricity and room air-conditioning. Pipework, light fittings and other services should be sited to avoid recesses within the processing areas. Ideally all such services are set in service corridors outside production, where they can be accessed freely by maintenance personnel.

Drains should be avoided unless essential, but in any case, should be designed to prevent any back flows. Open channels are generally not suitable but, if there is no alternative, then they should be shallow enough to be easily cleaned and disinfected.

The quality of the air-handling system is of major importance, both in terms of the supply to the areas and the extract systems. This is important in order to control humidity and temperature, both for product quality and operator comfort. Monitoring and control of air-handling systems is discussed in Chapter 12 in relation to sterile areas. The same principles apply in non-sterile processing areas, although limits will tend to be less tight and are not clearly defined.

Lighting of production and packaging areas should be appropriate to the operations being carried out. This is particularly important in areas for visual inspection or where documentation is being read or filled in.

Control of cross-contamination

The main objectives of GMP are to prevent mix-ups between batches and to prevent cross-contamination. Throughout this section, some of the measures that are used for the latter have been discussed. These are briefly summarized below:

- The best way to prevent cross-contamination is to use a dedicated production area for each product. This may be necessary for toxic compounds or sensitizing compounds such as penicillin.
- However, in most cases, companies use multipurpose facilities for their whole portfolio of products. In this case, a validated, effective clean-down procedure is essential. Validated cleaning procedures need to be developed for each compound and for each area to ensure that all residues are removed.
- Facility design should incorporate airlocks, pressure differentials and dust extraction systems.
- Removal of contamination by the use of properly designed and maintained filters will also assist in preventing cross-contamination.
- The use of protective clothing is also important. Some areas will require dedicated clothing. This dedication may extend to the laundry procedures and equipment to be used.
- Frequently the simplest solution to the problem of cross-contamination is to use a totally enclosed process so that material cannot escape. However, this will often require very special design considerations for appropriate processing equipment.
- The use of residue testing systems enables the identification of residues to show if the area or equipment is cleaned to the standard required.
- The use of status labels for materials, areas and equipment is essential, and labels should be checked prior to starting any operation.

Equipment

Whilst the range of equipment that is used in the manufacturing and quality control of pharmaceuticals is very wide, there are a number of general principles that should be adhered to for all items.

Prevention of cross-contamination or mix-ups is of paramount importance. Problems of this nature are particularly found in tablet compression machines and in packaging machines, respectively. Equipment should be designed and operated so that errors are prevented from occurring. An example of this is the way in which batch numbers can be changed on a machine. If a labelling machine, for example, has a solid block that has to be removed to enable a new batch number to be set up, then physical checks can be done. However, if the batch information is changed electronically, using a keyboard, it is necessary to ensure that inadvertent changes cannot occur.

Equipment should be operated in such a way that any quality problems are spotted as quickly as possible. Once again, compression machines are a common source of problems, particularly at start up and shut down. As the speed changes, so does the weight of the table and it is possible that out of specification tablets may be produced. Procedures should be in place so that, if this does happen, action is taken. Ideally, this issue should be resolved during equipment qualification.

Build-up of dust and dirt can occur unseen in some machines and eventually problems are found. Cleaning procedures should be effective enough to prevent this from

happening. Equipment must be able to be easily cleaned. It is important that all the necessary tools and equipment are available for equipment cleaning.

Equipment must be maintained to ensure that it performs correctly. A company should develop maintenance schedules and ensure that there are sufficient, trained personnel to carry them out. All use of the equipment, including maintenance activities, should be recorded in log-books.

Much production equipment relies on good quality services in order to perform correctly. If incorrect pressures or incorrect quality standards are available, acceptable performance will not be achieved.

Whilst being relatively simple pieces of equipment, balances and other measuring equipment are often sadly neglected. If a company does not provide its personnel with the appropriate measuring equipment, then GMP cannot be complied with and the quality of the product will be compromised.

Measuring equipment must be checked regularly for its ability to work within the specification and proper records (usage, check weighing, calibration) should be maintained. This generally means that check weighing should be done at the start of each day before weighing commences.

Equipment design

Production equipment must be appropriately designed for the job that it will carry out. For example, using the liquid-filling equipment to fill larger or smaller volumes than specified could lead to inaccurate volumes being dispensed.

The materials of construction of the equipment must be appropriate, particularly in the parts that come into contact with the product. In the pharmaceutical industry, this often means high-quality stainless steel or glass, although other materials may also be acceptable. Compatibility means that the product neither absorbs anything from the equipment nor reacts with it. The material of construction should also be good enough to resist the effect of the machine operation. If the machine uses a scraper blade for example, this should not cause damage to the surface being scraped nor should the blade be damaged. A frequent source of black specks in tablets is excessive lubrication of punches and dies on tablet-compressing machines or insufficient lubrication. Grey contamination of creams or ointments can come from bearings or plastic scraper blades that are incorrectly adjusted.

The equipment must be designed for easy cleaning, particularly if it will be used for more than one product. This means that the equipment should be easy to take apart; crevices should be designed out if possible and it should be easy to inspect the machine.

Maintenance and repair

Maintenance is an important issue. Ease of maintenance should be one of the criteria used when selecting equipment. Part of the purchasing specification should be for maintenance requirements and spare parts lists, together with any special tools that will be required. It is important that the maintenance instructions are written in the local language so that they can be read by the mechanics.

The equipment must be correctly labelled at all times. This will show whether it is clean or dirty, and whether it is dry or wet.

If equipment becomes defective for any reason, it must be clear from the status label, even if the equipment cannot be removed from the area. This will ensure that faulty equipment cannot be used by mistake. Where equipment is part of an in-line process and it is defective, then its connection to other machines in the line should be broken.

4.7.4 Documentation

Purpose of documentation

Documentation is an essential part of QA and relates to all aspects of GMP. The pharmaceutical industry must have a good document framework (infrastructure) and it is as important for a manufacturer to get the documentation right as it is to get the product right.

There are a number of purposes for documents:

- They are used to define specifications for materials and for methods of manufacture and control.
- They ensure that everyone knows what to do and when to do it.
- They allow decisions to be taken on batch release.
- They provide an audit trail, which is particularly important in the case of suspect batches.

Design of documentation

In terms of design, there is no one right answer; every company will have its own design(s) for documentation. However, it is better for the operators if a consistent approach is taken. It is possible for some of the documents to be combined, but generally they should be separate. They must comply with the relevant part of the manufacturing and marketing authorizations. All documents should be unambiguous with a title and a clear statement of purpose. They should contain clear, numbered references to each activity; have sufficient space to record relevant data; be easy to check; and all relevant activities should be recorded on them.

The master copy of any document should be signed and dated. Signatures will usually be those of the author and one or more approvers. There must be an effective change control system to manage the updating of documents, ensuring that all changes are recorded and operators are only using the current version.

Storage and distribution

Some documents may be stored electronically. Special controls will have to be developed that will satisfy the national drug regulations. Whichever way the master copy is stored, it is important that clear copies are reproduced for use with individual batches.

Distribution of documents needs to be carefully controlled in order to ensure that the most up to date version is always being used. There should be a distribution list if appropriate, attached to the document. Unauthorized photocopying of original documents should be actively discouraged. Some companies manage this by having part of the front page printed in colour, or by using an official stamp or other means of identification.

There should be an SOP for distribution, retrieval and preparation of documentation. A document register is required. This ensures that change control over all documents is managed.

Document review

Documents should be reviewed regularly; however, the definition of regular will vary with the company and with the document in question. Although not a requirement in GMP texts, it is useful that all master copies should have a review-by date. Alternative methods of identifying the need for review include diaries or electronic reminders. The key issue is to have a system.

Once the review date is reached, if no changes are required, the document should be annotated to show that it has been reviewed and the review-by date amended. If amendment of the document is required, there should be a history of the changes attached at the end. In the case of changes being made, it is important that all old copies are withdrawn and replaced by the new ones. (This confirms the previous point about the need for controlled distribution.)

Completion of documents

If the document is a process record, it should be filled in clearly and legibly. The writing should be indelible, i.e. in pen, not pencil. Any alterations must be made by drawing a single line through the incorrect information, signing it and putting in the new information. There should be no use of correcting fluid or similar products. If alterations are made, then the reason for the alteration should also be given. This is particularly important where a laboratory test result is changed. The reason for the change must be given.

There should be no blank spaces left on a document. If a box is provided for inputting information, it should either be filled in or marked as not applicable. To leave it empty causes problems for the people auditing the documents: they will not know whether it should be blank or not. All associated charts and other materials, such as sterilization records and copies of printed packaging materials, should be included with process records and stored with them.

It is essential that documents be filled in as the process proceeds: completing them in advance involves guesswork, and filling them in retrospectively relies on a photographic memory. Neither is a substitute for keeping accurate timely records.

Labels

There are two classes of label used in the pharmaceutical manufacturing facility. There is the finished product label, which must meet national drug regulatory authority requirements as specified in the marketing authorization. Then there are the labels used within the factory to control the process. These will be internal systems, designed by each individual company.

Labels are required for all containers of material, whether starting materials, intermediates or finished products. There must also be sample labels and labels that are applied to materials that have been sampled, and labels for all process equipment and for premises that are in use for manufacturing. All labels should be clear and unambiguous. Where possible, it is advisable for companies to use colours to indicate status (quarantine, accepted, rejected, cleaned or dirty).

Responsibility for labelling will vary with company practice, but the process will generally be overseen and controlled by QC. They will be responsible for the issue of status labelling when a material has been approved or rejected. Production and/or QC should sign labels stating that equipment is clean and available for use.

Reference standards (both primary and secondary) must be appropriately labelled and the issue of these must be controlled.

Specifications and test procedures

Test procedures must be validated or verified for the available facilities before they are used for routine testing. Compendial methods need to be verified. This means that the method is demonstrated to give correct results in the laboratory facilities available. Specifications will include tests for identity, content purity and quality. Specifications should be dated and authorized. The responsibility for their issue and maintenance rests with QC. It may be necessary to update the documents occasionally in line with the national compendia or the company's requirements.

Specifications are required for all starting and packaging materials, including water in all its various standards. There will be a certain amount of information that is mandatory, according to the relevant GMP text; additionally there will be other information that the company chooses to add.

For packaging materials, there should be reference to compatibility with the drug. For all materials, the frequency of retest should be specified.

If intermediates or bulk products are either purchased or dispatched, then they will need a specification. One will also be required if the data obtained from these materials are going to be used in the assessment of the finished product. They will be similar to the specification for the starting material or finished product as appropriate.

For finished products, the specification will include the following information: the designated name and internal code reference; the designated name of the active ingredients; the formula (or a reference to it); a description of dosage form and packaging; the sampling and testing methodology; the test parameters and acceptance criteria; the storage conditions; and the shelf life.

Specifications and test procedures will be used by QC and will generally be located in the laboratories.

Master formulae

There must be a formally approved master formula for each product that is manufactured, in each batch size. The information that it will contain will include the name of the product, dosage form, the bill of materials, methodology of manufacture and storage requirements.

The packaging instruction is the equivalent of the master formula, but it covers packaging rather than manufacturing. There should be one document for each product and pack size. The information that it will contain will be similar to that listed above.

Both these documents will be used as reference in the development of processing records. They will be located in development departments, in QC and with production.

The master formula is frequently used as the master batch-processing document. It is often photocopied to provide the individual batch-processing document. Whatever method is used, it must ensure that there can be no transcription error. The batch processing document is never a hand-written copy. The same method can be used to prepare the batch packaging document.

Batch processing records

A batch processing record is required for each batch of material produced. The review of this document is a critical part of the batch release process. A master document should be

prepared for each batch size that will be manufactured. It will be taken from the relevant parts of the master formula as discussed previously.

The first step in this document must be the area clearance check. This is a record of the previous product and batch processed in the area and a confirmation that all the material and documentation relating to that batch has been removed. It is also confirmation that all the cleaning has been carried out correctly. This check must always be documented.

The batch processing record is both a detailed instruction to the operator of the activities that must be carried out during manufacturing and a record that those activities have been carried out. It should be filled in at the time that processing takes place. Critical activities require a check signature from a second person (either from production or QC as appropriate) to confirm that the information recorded is accurate.

Information that does not change, such as the product name, process steps and theoretical quantities of material, will be printed on the master copy. Variables such as the actual quantities of materials used and yields will be entered by the operators during the manufacturing process.

Batch packaging records

The batch packaging record is required for every batch or part batch that is packaged. It is developed from the relevant part of the packaging instructions and, once again, its review is an important part of the batch release process. Depending on company practice and the design of the document, it may be specific to a particular batch size or may be used for a variety.

Comments made previously regarding area clearance checks also apply here. Use of a checklist for these checks is very helpful. Looking under tables and checking for extra labels or primary containers are very important.

The information required for the completed batch packaging record will once again consist of a combination of pre-printed material and data that are added by the operators during the process.

If returns to the stores are permitted for printed packaging materials, they should first be checked to make sure that they have not been batch coded. A QC signature is required as part of this process, either on leaving the packing hall or being received in the stores.

If excess materials are destroyed, there must be a record of the quantities on the batch documentation. There should also be a procedure covering destruction, including methods and responsibilities.

Reconciliation is of vital importance, since it helps to confirm that the batch has been processed correctly. Any significant variation in materials should be taken as an indication that there could be a problem and must be investigated before the batch is released.

Standard operating procedures

SOPs are required for a whole range of activities within the facility. They tend to relate to activities that are not product specific. For example, whilst a batch processing record will provide details of how to manufacture a batch of product X, the SOPs will provide details of how the equipment that is required to produce product X is operated and cleaned.

Although useful reference documents for inspectors, SOPs are primarily written for the benefit of the persons carrying out the operation in question. They should be written so

that the user can easily understand them. If possible, they should be written by or with the operators, to ensure that they accurately reflect what happens in practice. They will be written by the department responsible for carrying them out, but should also be approved by QA if appropriate. It should go without saying that they should be written in the local language. Sadly, from experience, this is not always the case!

Master copies of procedures should be stored by the responsible department or centralized in the document control department. Authorized copies of each procedure should be stored adjacent to the place where the operation will be carried out, as a reference document that can be consulted at will.

All critical equipment should have log-books in which maintenance and cleaning are recorded. A record should also be kept of the usage of this equipment.

Stock control records

Stock control documentation is required for raw materials, packaging materials and finished products. The records include batch numbers, status, quantities and the expiry date. They may be manual or electronic, but must take into account the status of the batch in question. They ensure an appropriate system of material rotation, such as FIFO (first in, first out) or FEFO (first expired, first out). The records will be validated by the physical stock check carried out periodically in the warehouse.

For distribution, there should be one record per batch of material. It should contain the batch number, quantity and destination of each delivery. Hence in the case of a product recall, the information on distribution can be obtained rapidly from a single source. Using copy invoices as distribution records is *not* advisable unless the batch number is recorded. If a computer-controlled stock management system is used, this can provide a very acceptable method of recording distribution.

4.7.5 Production

Materials

The main function of the pharmaceutical factory is to combine different materials to produce a finished product. The systems that a company operates to control all the materials are of vital importance to the quality of the finished product.

Material management is important throughout all the stages: specifying the materials; buying materials; receiving materials; storing materials; dispensing; using materials; storing the finished product; distributing the finished product; and dealing with all the reagents used in testing, the standards used in testing and the waste materials that arise from the processes.

If GMP is not correctly applied, the company may have to handle the problems caused by returned goods, rejects or recalls. It is mandatory that materials be handled in a way that meets GMP requirements.

General principles

There are some general principles to be considered regarding material management. Incoming materials and finished products should be quarantined immediately after receipt or processing until they are released for use or distribution.

The manufacturer should store the materials in conditions established by the supplier as being correct for that material. This means that the storage conditions must be known and achieved. Conditions should be monitored to ensure that parameters stay within the specified values. Batches must be correctly segregated and stock should be rotated on a FIFO or FEFO basis.

When considering starting materials, GMP should start with purchasing. Personnel with the technical knowledge of the requirements of each material must be involved in the purchasing decision. They should also have a thorough knowledge of suppliers and products. Purchasing should no longer be considered as just a simple financial transaction. Starting materials should only be obtained from the suppliers listed on the relevant specification. If at all possible, the materials should come direct from the manufacturer. The specification must be discussed initially with the proposed suppliers, to ensure that they are able to make a commitment to supplying a material routinely that will always comply with the specification required. All aspects of the supply should be discussed and agreed upon. This will include all matters relating to manufacture and testing of the material by the supplier, labelling, packaging, complaints, rejection procedures, as well as shipping requirements. The value of a well-designed and agreed specification cannot be underestimated. The creation of such a specification is a technical matter that is best undertaken in partnership with suppliers. It is not a financial matter, although clearly, there will be financial implications arising from the discussions.

Receipt of materials

As consignments arrive, the containers should be checked for compliance with the order. The containers should be checked for leakage, damage and contamination as necessary, and cleaned and labelled with the prescribed information.

Any damage that is observed should be recorded and reported to both QC and to the purchasing department. If a delivery of one material is made up of several batches, then each batch should be treated separately for sampling, testing and release. If this is not done, for example, if all subbatches are tested but there is no separation of bulk materials, then all the materials will have to be treated as one batch. This means that failure of one subbatch will mean rejection of the whole delivery. This situation may arise with the use of bulk storage silos for some materials. Procedures should be available to describe the sampling routines that will be followed for each material. The containers from which samples have been drawn should be identified.

Starting materials in the storage areas should be properly labelled. The labels should carry at least the following information: the name of the material and internal code reference; supplier batch number and manufacturer receiving number; status of contents; expiry date; and date for retest.

If computer systems are used to control the location and movement of materials, not all of this information needs be in a human-readable form. Bar codes are now frequently used to deliver such information. If these systems are used, they must be validated.

The QC department has the responsibility to release (or reject) material for use. Only materials that have been so released, and that are within their shelf life, should be used.

Dispensing

The materials needed for manufacturing should be dispensed by qualified and trained people who are following written procedures. Dispensing of materials is a critical stage of

manufacturing and therefore requires very particular care. The materials are now at one of their most dangerous stages in manufacturing. They have been taken from a clearly labelled container and are being placed into a smaller container for use. The containers into which the dispensed material is placed must be clean and properly labelled. Dispensing of materials for a batch of product should be done one material at a time, to prevent cross-contamination or mix-up.

The weight or volume of material and the batch number of the material should be independently checked. Other items should also be checked, including expiry date of material and identification.

All the materials required for a batch should be brought together and kept together until they are needed. They should be clearly labelled as to their intended use.

Packaging materials

The term packaging materials refers to all primary packaging components as well as all printed materials. So the same principles apply to bottles and ampoules for example, as much as they do to labels, cartons, blister foil and so on. Generally, packaging materials should be handled in the same way as any other starting material.

Particular attention, however, must be paid to printed components. In some countries, over half of all product recalls are the result of failures in the quality of printed components. Hence security is essential. Cut labels and other loose printed components should be stored and transported in separate closed containers to avoid mix-ups. Any printed components rejected on receipt should not be returned to the supplier but physically destroyed at the factory after notifying the supplier. The QC department should witness the destruction. The supplier may wish to examine the materials before destruction. Allowing the supplier the opportunity to do this should not prolong the process of destruction.

Packaging materials should only be issued for use by authorized persons, to authorized persons, following a written procedure.

Every delivery or batch of printed components should have a specific reference number or batch identity. A packaging component identification mark is valuable to identify the version of the component.

Any obsolete or outdated packaging materials must be destroyed and its disposal recorded. This is essential to prevent unauthorized use of these components. There have been many cases of counterfeiters, who have successfully removed waste or obsolete packaging components illegally from companies, and then used the materials in their own products.

When the packaging department receives a delivery of materials, these should be checked for conformance with the requirements in quantity, quality and identity.

Intermediate materials and finished products

Intermediate or bulk products refer either to those materials or products that are prepared en route to the finished product or, for example, bulk tablets before they are packed. In all cases they should be appropriately stored. On receipt, they should be handled just like any other starting materials.

Finished products should be held in quarantine until quality assurance has released them for distribution. All storage should conform to the conditions specified in the marketing

authorization so that it maintains its safety, efficacy and quality throughout its predicted shelf life.

Rejected materials

Any rejected materials should be clearly marked as such and stored separately in a restricted area. Materials that have been rejected should be returned to the suppliers, reprocessed or destroyed. Too often, people store such materials in the hope that at some time they may be accepted. A strictly enforced maximum allowed time in a rejected store is often helpful in ensuring that materials are moved on quickly. All actions should be recorded.

Rejected materials may be reprocessed. However, this should be exceptional. Since it is exceptional, then a clearly developed process will be required. It may only be done if the quality of the finished product is unaffected, all specifications are met and all the risks have been assessed. Batch records will be required, and the reprocessed batch will need a new identifying number. The inspector should question the company to ensure that all relevant aspects have been considered.

Recovery or 'working off' of materials may also be acceptable. It should be approved by an authorized person and be in accordance with a developed procedure. The procedure should include consideration of the effect on shelf life. The procedure to be followed must be in accordance with local legislation. Records will be required of the recovery procedure including the amounts of recovered materials and the batch numbers.

Recalled or returned materials

Products that have been recalled from distribution need to be clearly identified as such and stored in a segregated place that is secure. They should be stored there for as short a time as possible. The action to be taken with them should be developed as quickly as possible in accordance with the written SOP and the action implemented without delay. Every care must be taken to ensure that they are not redistributed by mistake.

Products may be returned from the distribution chain for reasons other than recall. These products are known as returned goods. Before they may be returned for distribution, QC should be able to re-examine them and take a decision concerning their suitability to re-enter the distribution chain. The system for handling returned goods should be described in a written procedure.

Laboratory materials

All reagents and culture media should be recorded on receipt or preparation. Any reagents made in the laboratory should be treated, in effect, like products. They should be made in accordance with written procedures and labelled properly. The label should contain all the standard information, and be signed and dated by the person making the reagent.

Reference standards may be available as official reference standards. Any substances produced should be stored in a secure place as the official standards. Official standards should only be used for the purpose described in the official monograph. All in-house standards should be based on official standards when they exist. Working standards may be developed, provided they are subject to all the tests at regular intervals to ensure standardization. All standards must be stored under specified storage conditions so that their quality is unaffected.

A log-book for preparation and use of reference standards is essential to demonstrate traceability of preparation.

Waste materials

All waste materials that are awaiting disposal must be kept in the conditions that are secure and, as necessary, meet national legislation, particularly for safety. Some of these materials may be toxic or flammable. Waste material must not be allowed to accumulate. It must be disposed of in the agreed way regularly and frequently.

There are all sorts of other materials in a pharmaceutical factory. They should all be there, fulfilling a specific purpose. These are items such as rodenticides, insecticides, fumigants and cleaning materials. They must be prevented from contaminating the facility, including machines or production materials and the surrounding environment. These materials are frequently toxic and poisonous, and must be carefully controlled to prevent accidental inclusion into a product.

Validation

The topic of validation is a very important one that deserves a lot of careful thought. This section merely presents an overview. A good starting point is the principle that a bad process cannot be validated.

There are a number of definitions of validation, all of which say the same thing in different ways. The definition given in the EU guidelines is as follows: 'action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification)'. In other words, validation is the establishment of documented evidence that a system does what it is supposed to do.

There are three key points to take from these definitions.

- The evidence must be documented. If it is not written down, it did not happen.
- It applies to all aspects of manufacturing, from process development onwards.
- The evidence requires that the system does what is expected of it.

In other words, validation is carried out against a set of criteria that are defined in advance. These criteria are detailed in pre-defined protocol documents. Validation is required when a process is first established, when significant changes occur to the process and periodically thereafter.

Process validation

Process validation requires the identification of critical elements and includes equipment qualification. There are a number of different types of process validation.

Prospective validation is carried out during the development stage. It divides the production process into separate steps and carries out analysis on potential critical situations. These situations are defined on the basis of past experience. Trials are carried out in which these critical situations are simulated and the effect on the process is assessed.

Concurrent validation is carried out during normal production. It requires a full understanding of the process based on prospective work and involves very close monitoring of at least the first three production-scale batches.

Retrospective validation is the use of accumulated results from past production to assess the consistency of a process. It will include trend analysis on test results and a close examination of all recorded process deviations.

It is important to have a sufficient number of batches manufactured over a specified period of time to provide a statistically significant picture. As a technique it does not check the limits of the process. Hence, it is not the preferred approach.

Revalidation

Revalidation is divided into two categories: revalidation after a specific change; and periodic revalidation. In the former category, typical changes that require revalidation include changes in a raw material or packaging material, changes in the process parameters, changes to equipment, including major repairs and changes to the premises.

Revalidation would also be required for any changes resulting from a failure investigation. Corrective actions deemed necessary after such an investigation must be brought under the change control procedure, which will determine what aspects of revalidation are required.

A periodic revalidation is the opportunity to check that the systems are still operating as originally validated and that no 'drift' (unobserved or unintentional process changes) has taken place over time.

Cleaning validation

Cleaning validation is needed in particular for multipurpose equipment. It should be performed using the worst-case situation of product changeover. For example, products that are difficult to clean or are active at very low concentrations would be chosen as exemplars.

Validation in established factories

Having reviewed the definitions, consideration should be given to what the situation is likely to be in reality. For a new facility, there should be a programme of validation that covers the installation, commissioning and start-up phases. This will be a combination of prospective and concurrent validation.

However, for most facilities that have been established since before validation was introduced, there will be a gradual process of retrospective validation. This should be based on an assessment of the critical processes and allocation of priorities. For example, a sterile product is more critical than a tablet and the sterilization step will be the one that should take priority in the validation programme. Even in these older facilities, the introduction of new products should be accompanied by prospective and/or concurrent validation.

Stages of validation

For any validation project, there will be a number of stages that must be worked through before validation can be said to be complete.

Design qualification (DQ) is the process of completing and documenting design reviews to illustrate that all quality aspects have been fully considered at the design stage. The purpose is to ensure that all the requirements for the final systems have been clearly defined at the start. In other words: has it been designed and selected correctly?

Installation qualification (IQ) is the process of checking the installation to ensure that the components meet the approved specification and are installed correctly, and how that information is recorded. The purpose is to ensure that all static aspects of the facility or equipment are installed correctly and comply with the original design. In other words: has it been built or installed correctly?

Operational qualification (OQ) is the process of testing to ensure that the individual and combined systems function to meet agreed performance criteria and recording the results of that testing. The purpose is to ensure that all the dynamic attributes comply with the original design. In other words: does it work correctly?

Performance qualification (PQ), also called process qualification, is the process of testing to ensure that the individual and combined systems function to meet agreed performance criteria on a consistent basis, and how the result of testing is recorded. The purpose is to ensure that the criteria specified can be achieved on a reliable basis over a period of time. In other words: does it produce product correctly?

There are three types of documents related to validation: master plans, protocols, and reports.

Validation master plans

Each company should have a validation master plan (VMP), which describes its overall philosophy, intention and approach to establishing performance adequacy. The VMP also identifies which items are subject to validation, and the nature and extent of such testing. It defines the applicable validation and qualification protocols and procedures.

The VMP is the overall planning document that details what should be covered during the programme, i.e. it covers who, what, where, when, why and how. It includes a breakdown of the process, plant or equipment into separate parts. It also determines which of these are critical to the quality of the product and therefore require validation, and at which stages. For example, in a project to commission a sterile manufacturing suite: the operation of the sterilizers are critical and will require IQ, OQ and PQ; the operation of the ventilation system is critical and will require IQ, OQ and PQ; but, although the layout of the suite is important, it could only require IQ.

The VMP should be a concise and easy to read document, which will serve as a guide to the validation committee and personnel who are responsible for implementing validation protocols. The VMP should also be viewed as a source document for use by regulatory auditors.

The VMP will always be a brief overview, as well as being a dynamic document, as many details are not finalized at the start of a project. However, if the plan is changed, it must be done under an effective change control procedure.

Validation protocols

A validation protocol is a detailed document relating to a specific part of the validation process, e.g. the OQ for a manufacturing vessel. It outlines the tests that are to be carried out, the acceptance criteria and the information that must be recorded. It will also define the approval process for the validation.

The protocol should clearly describe the procedure to be followed for performing validation. The protocol should include at least: the objectives of validation and qualification study; the site of the study; the responsible personnel; a description of equipment to be used (including calibration before and after validation); and the SOPs to

be followed. The standards and criteria for the relevant products and processes, and the type of validation and time/frequency should also be stipulated. The processes and/or parameters to be validated (e.g. mixing times, drying temperatures, particle size, drying times, physical characteristics, content uniformity, etc.) should be clearly identified.

Validation reports

The validation report is the final collection of test results and other documents such as instrument calibration certificates. It is on the basis of this report that the decision is taken on whether a particular process is judged to be valid. A written report should be available after completion of validation. The results should be evaluated, analysed and compared with acceptance criteria. All results should meet the criteria of acceptance and satisfy the stated objective. If necessary, further studies should be performed. If found acceptable, the report should be approved and authorized (signed and dated).

The report should include the title and objective of the study, and refer to the protocol, details of material, equipment, programmes and cycles used, together with details of procedures and test methods. The results should be compared with the acceptance criteria.

Included in the final report should be recommendations on the limits and criteria to be applied to all future production batches. The report could form part of the basis of a batch processing document.

It is common practice in many companies for the protocol and the report to be combined into a single set of documents. The protocol is approved as a pro forma into which the test results are recorded as they become available. This reduces the amount of paperwork that needs to be stored and makes an overall assessment of the validation results easier to carry out.

4.7.6 Contract manufacture and analysis

The global industry is changing its shape through rationalization, mergers and acquisitions. Companies are increasingly considering the use of other manufacturers to produce or manufacture their products. Companies are also finding that they do not have the technology or expertise to manufacture certain new formulations coming from research. In some cases, aggressive financial targets mean that companies are not using manufacturing as a core business process. This means that the importance of contract manufactured and tested products is also increasing. It may also mean that companies no longer have their own technical expertise to fulfil all the requirements for GMP and control over their sources of supply.

Increasingly many companies in developing countries are used as contract acceptors. It is important for all involved to understand the principles involved and the detailed mechanisms required for managing contract work properly.

The principle that is to be used for contract production and analysis is very simple. The work has to be clearly defined, agreed and controlled to avoid misunderstandings. If misunderstandings arise, then work may be done that does not meet the quality standards set.

The contract

The simplest way to avoid such misunderstandings is to have a written contract, setting out the duties of all parties to the contract and the standards that must be met. The

standards of performance refer not only to product quality standards but also to delivery performance costs and many other non-GMP aspects.

It must be clear who is the authorized person, having the responsibility and the final authority to release a batch for sale. The authorized person must be involved in setting up the contract and agree to the way in which information will be provided, that will allow him/her to make a decision to release a batch of product.

The most important issue to be considered is that any work done must be in compliance with the registered marketing authorization. If a product is transferred from its existing location to a new contract location, then it is likely that the product will be manufactured using equipment that is different from that appearing in the product registration file. Such changes of manufacturing process or conditions may need the approval from quality assurance and/or the regulatory authority before implementation. The contract giver must ensure that the contract acceptor has a valid licence to manufacture the product under contract.

The contract giver

The contract giver must have the right to audit the premises of the contract acceptor. This is to assess compliance with GMP and to ensure that the premises and equipment will provide product that meets the requirements of the marketing authorization. It will also permit the contract giver to identify those areas where they may be able to contribute practical product knowledge to the staff of the contract acceptor.

In the case of contract analysis being carried out, the product must only be released for sale by the authorized person for the product. This must be clearly specified in the contract. The national laws for different countries may modify exactly how this is applied.

There are a number of aspects that are the responsibility of the contract giver. Firstly, they are responsible for assessing the competence of the proposed contract acceptors. The contract giver will normally know the product better than any one else. This will be the case if the contract giver has developed the product. They know the work that needs to be done. They must assess whether the firms that offer to do the work really have the capability to do it. This assessment must also include a review as to whether the contractor is able to operate to the appropriate GMP principles.

Once the conclusion has been reached, that the contract acceptor has not only the technical competence but also the GMP competence, then the contract giver must provide a full technical information package to the contract acceptor.

This should enable the contract acceptor to make the product safely and in accordance with the marketing authorization. This means that all the information relevant to people, premises and equipment must be provided. If there are hazards associated with cross-contamination or other products, these must also be highlighted.

Finally, the product made or tested under the contract must only be released by the authorized person in compliance with the marketing authorization. In some cases the authorized person may be the contract acceptor, if this responsibility is delegated in writing by the contract giver and if such delegation is permitted by national regulations.

The contract acceptor

Similarly, the contract acceptor also has responsibilities. The company must be competent to do the work. This means that their staff has the necessary qualifications, training and experience. It also means that they have the appropriate facilities, premises and

equipment, both in type and in quantity, to undertake the work. It means that they have a manufacturing authorization to do this type of work.

The contract acceptor may not pass the work or any part of it on to a third party (subcontractor) without the approval of the contract giver. In order for the contract giver to be able to accept a third party, they must be able to undertake all the audits that they need to reassure themselves that the third party is competent. All the responsibilities placed upon the contract acceptor must be fulfilled by any third party contractor that may be employed.

Finally the contract acceptor must not then undertake new work, which may adversely affect the quality of the existing products. An illustration of this would be to take on work to make a non-penicillin product and then accept the manufacture of a penicillin product in the same facility.

The contract that is prepared between the contract giver and the contract acceptor must identify clearly the responsibilities each has with respect to the relevant sections, and the work to be done. All the technical details and specifications must be prepared by competent technical staff. All the arrangements must be made in accordance with the marketing authorizations and agreed by both giver and acceptor.

The contract must be very clear about the way in which the authorized person will approve the product for sale. It must enable the authorized person to check that each batch has been made in compliance with the marketing authorization.

Product release

The contract must specify who is responsible for the purchase and testing of all incoming materials and their release to production. It must also specify the in-process testing that is to be done and who is responsible for sampling and analysis. In the case of contract analysis, the contract should specify whether the contract acceptor is responsible for sampling, and if so where the sampling is to be done. If contract analysis is being undertaken, then the contract must show how the information will be processed and in what time span it will be done.

All manufacturing, analytical and distribution records, and reference samples must be kept by or be made available to the contract giver. Any records relevant to assessing the quality of a product in the event of a complaint or a suspected defect must be accessible to the contract giver. These records must also be specified in the defect/recall handling procedures used by the contract giver. This is to ensure that, in the event of the need to recall the product, the contract giver can immediately access the necessary records.

The contract should also specify clearly what would happen to materials that are rejected.

4.7.7 Complaints and recalls

Complaints

One necessary but not always pleasant aspect of quality management is dealing with complaints.

Complaints must be handled positively and be carefully reviewed. Actions must be taken as necessary, possibly even leading to a recall decision. The handling of complaints

must be seen by all areas of the company as being important work, which is the responsibility of a senior staff member.

Thorough investigation of the cause for the complaint is essential before decisions can be taken as to the resolution. Complaints can be an important source of learning for the company and enable potentially serious defects to be remedied before they become so serious as to initiate a recall.

Complaints procedure

It is important that the people handling complaints do so in accordance with a written procedure, and that the results of the investigation are used to the advantage of the patient and the company. All companies should have a written procedure for dealing with customer complaints. This procedure should describe all the actions that need to be taken and by whom.

The complaints procedure must be written, authorized by at least the QC manager, describe clearly the actions to be taken and include the need to consider a product recall if the type of complaint necessitates such a decision.

A responsible person must be designated who has the authority to conduct the complaint review in accordance with the procedures. The person designated may be the authorized person responsible for QC. If not, then that QC person must be kept informed of all complaints being investigated. The designated person must have sufficient staff to be able to review all the complaints received in an effective and rapid manner. They have to be able to access all the relevant records concerning the product under discussion.

Complaints records

Besides the complaints procedure itself, full records should be kept to document each incident. The records should include not only written communication, but also verbal correspondence, such as initial phone calls. These records can then be used by senior management to change the necessary processes within manufacturing or QA to ensure that the complaint does not arise again.

Response to complaints

All complaints should be fully investigated. The investigation should be thorough enough to identify the fundamental cause for the complaint. Only then will the opportunity arise for corrective action to be taken.

A complaint (assuming it is justified) may be the result of a one-off incident. Alternatively, it may be indicative of a trend related to one product or the process that is used to manufacture a number of products. It is important that complaints are not considered in isolation, but as part of the bigger picture. It may be necessary to consider whether other batches should be checked to see if they too should be subject to detailed investigation.

It is important in the management of each complaint that the company should acknowledge its receipt and respond to the complainant. There are two possible outcomes of a complaint investigation: either it is found to be justified or it is found to be unjustified. In either case, there are implications for further action.

If the complaint is justified, there should be mechanisms in place to ensure that the problem does not reoccur. The complainant must be notified. It is assumed that the

defective product will have been replaced previously but, if not, replacement should happen at this point.

On occasion, it will be found that the complaint will not be justified. In this case, the complainant must be advised of the fact. There can be cases where the complaint, whilst unjustified, was genuinely made. On other occasions, there can be malicious intention behind the complaint. Once the investigation has been completed satisfactorily, it is no longer a technical/GMP issue. At this point it becomes a commercial/marketing issue as to how the individual is treated. The response to the complainant may be different depending on company culture and local practice.

Recalls

Whereas complaints tend to centre on individual doses of product, a recall situation is where there is perceived to be a problem with an entire batch and it is all withdrawn from the marketplace. Recalls occur when a batch or batches of product are found to have critical or major defects associated with them.

A critical defect is one that could be life threatening and requires the company to take immediate action by all reasonable means, whether in or out of business hours. This means that all wholesalers must be alerted and actions taken at any time to commence recalling the product throughout the distribution chain. It may mean using radio and television announcements to carry out the recall.

Examples of such defects would be: a product labelled with an incorrect name; a counterfeit product or one that had been deliberately tampered with; and microbiological contamination of a sterile product.

Major defects are those which can put a patient at some risk but are not life threatening, and will require the batch recall or product withdrawal within a few days. In some countries this is specified as within 48 hours.

Examples of such defects would be: any labelling/leaflet misinformation (or lack of information) that represents a significant hazard to the patient; microbial contamination of non-sterile products, which may have medical consequences; and non-compliance with specifications.

Recall triggers

There are a number of different ways in which a recall situation can be triggered.

- Customer complaints: if a complaint reveals evidence of a critical or major defect, it can lead to a recall. This could also happen if there were a significant number of complaints about one particular product or process.
- GMP deviations or results of a failure investigation: if a company carries out an investigation as a result of problems during processing of a particular batch, it might lead to the discovery of problems with earlier batches that were not detected prior to release.
- Result from the QC stability programme: for example, if the stability studies showed unusual deterioration of activity within the normal shelf life of the batch.
- Information from the regulatory authorities: on occasion, complaints are sent to the authorities rather than directly to the company; in addition, random samples are taken from time to time from various parts of the distribution chain.

- Result of an inspection: if a regulatory inspection uncovers a problem with the manufacturing process that casts doubt on the validity of the release for a given product.
- Known counterfeiting or tampering with the product: if it is known that counterfeit product has been released on to the marketplace, it may be necessary to withdraw all the product until it can be established which is the genuine product.
- Adverse drug reaction (ADR): ADRs, reported as part of a pharmacovigilance programme, can but will not automatically lead to a recall situation.

Whilst complaints are a fact of life and will occur in all companies, the situation of a recall is one that all companies hope to avoid. As can be seen from the list above, it may not always be the fault of the manufacturer. However, whatever the reason for the recall, the company must be prepared with appropriate procedures in place.

Recall procedure

The company must have a procedure in place that can be operated at all hours to decide if a defect warrants a recall and what level of urgency there is.

As before, there must be a responsible person designated as recall co-ordinator, with the authority to conduct the recall in accordance with the procedures. The person designated may be the authorized person responsible for quality control, but if not the QC person must be kept informed of all recalls being conducted. The designated person must have sufficient staff to enable them to undertake the recall in an effective and rapid manner with appropriate urgency. The designated person should normally be independent of sales and marketing organizations, and must have the status and authority to be able to carry out the procedure.

Since recalls do not always occur at convenient times of the day or the year, it is important that the procedure includes contact details for the designated person and that there is also a nominated deputy to cover for holiday or sickness absences.

The recall procedure must be written, authorized by at least the quality control manager, describe clearly the actions to be taken and include the need to be regularly checked and updated. It must be capable of rapid start-up, out of business hours, if necessary. It should include a communications plan with all key personnel and deputies in case of absence out of normal business hours. Key contact telephone numbers for all authorities that may need to be contacted should also be included.

Recalls and regulatory authorities

It is essential that all the authorities in all countries to which the relevant batch(s) have been sent are informed of the recall. This contact may be done government to government but it may not be. It is the manufacturer's responsibility to ensure that the competent authorities in each country are informed. The manufacturer should also inform the importer of the product. The importer will probably be the holder of any product registration and will also know where the product has been distributed.

In each country, the regulatory authorities may wish to make their own decision as to whether to initiate a recall. The decision may not necessarily be the same as the country that produced the product.

Recall records

Essential to the success of any recall is the quality of information contained in distribution records. The firm is required to maintain in its own records, accurate information on the quantity and batch number of any product it sends to wholesalers or its own direct customers. Full details of name, address and telephone number must be kept for all customers.

As the recall progresses in accordance with the procedure, written progress reports must be kept showing that all stages of the recall procedure have been adhered to. Reconciliation must also be prepared, showing the total product quantity distributed and the total quantity returned by batch. It should identify any areas where reconciliation has not been able to be achieved and offer reasons why. A final report must also be issued to cover all aspects of the recall including lessons to be learnt for the future conduct of such recalls.

The effectiveness of procedures must also be regularly checked and any lessons learnt from this process used to modify procedures accordingly. Testing of the effectiveness of the recall procedure can be done by conducting a dummy recall of a particular product. This involves identifying a batch and then conducting a paper recall only to test out the systems. Such dummy recalls should be done not only in normal office hours but also at the weekend and in the middle of the night to see what happens.

As goods are returned, they must be stored in secure storage away from all other goods until their fate is decided. It is also important that existing stock of the batch in the warehouse should be moved into this secure storage. This is very important because there must be no risk of confusion with other good product.

4.7.8 Self-inspection

The topic of self-inspection is fully covered in Chapter 11 on inspections and auditing.

4.8 Case studies

4.8.1 Case study 1

A long-established company in one of the CIS countries was producing a mixture of penicillins, cephalosporins and general pharmaceuticals within the same facility. As the country moved towards adoption of European standards of GMP, the company realized that it could no longer sustain this mix of manufacturing and began to examine its portfolio to determine the best way forward. It was decided that the general products should be removed to a separate facility and the penicillins and cephalosporins completely segregated from each other.

Reference was made to the EU guidelines in order to determine which products could be produced together. The management of the company was frustrated to find the following statement: ‘The production of *certain* additional products, such as *certain* antibiotics, *certain* hormones, *certain* cytotoxics, *certain* highly active drugs and non-medicinal products should not be conducted in the same facilities’ (author’s italics).

The management could not understand why the guidelines did not publish a full list of exactly which products were allowed and which were not. They could not see that such a list is dynamic and would be out of date almost before it was published.

4.8.2 Case study 2

Whilst presenting a training session for a number of government inspectors in a former Soviet country, the author became involved in a discussion on appropriate equipment for carrying out cleaning in a controlled environment such as a sterile manufacturing plant. The class reviewed the types of cloths, mops, etc. that were available and then wanted to know who was responsible, in Europe, for accrediting such equipment. In other words, who would have the authority to say that a particular piece of equipment could be used or not. The answer they were given was that, ISO and national standards notwithstanding, the main responsibility lay with the technical management team within the companies themselves. This was an alien concept to many of the delegates and caused a fair degree of consternation.

4.9 Summary

In this chapter, we have reviewed a number of the main reference texts used around the world for identifying the requirements of GMP in relation to the manufacture of pharmaceutical products.

We have seen that, whilst the approach and layout vary with different versions, the topics covered and the key principles are similar in all cases. However, the texts are in the main guidelines only. In other words, they describe what should be achieved, rather than how it should be done. The latter is often a question of interpretation and is the responsibility of the individual companies.

5

Good distribution practice

5.1 Introduction

Within Europe, the overriding documents that relate to logistics and distribution are the national regulations. In the UK, these are The Medicines (Standard Provisions for Wholesale Dealer's Licences) Regulations, first published in 1971, and subsequently amended five times up to 1993. However, these are legal documents, written in a form that is supposedly beyond question in terms of the legal process. As a result, they are fairly unreadable and are not particularly useful as reference documents.

The key quality requirements are outlined in the Council Directive 92/25/EEC Wholesale Distribution of Medicinal Products for Human Use, which is somewhat more readable. This directive is presented as 12 articles that deal with the following aspects of the requirements:

1 Definitions
2 Marketing authorizations
3 Conditions for marketing authorizations
4 Granting of marketing authorizations
5 Requirements for suitable premises and personnel
6 Obligations on wholesalers
7 Equivalent treatment in Member States
8 Documentation
9 Exceptions, relating to narcotics, blood products, immunological products and radiopharmaceuticals
10 GDP guidelines
11 Date and method of enforcement
12 Date of issue.

Resulting from this directive, a guidance document was issued in 1994: Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C63/03). This is the key reference document that should be used as the basis for developing or checking for compliance.

5.2 Principles of GDP

The guideline opens with a section that outlines the principles to be achieved. The first of these principles is that the products must have the appropriate quality. When a drug is first developed and launched on to the market, its quality is assured by the authorization for marketing. During manufacture, the maintenance of quality is ensured by the fact that the producer will have a manufacturing licence, relating to their compliance to GMP. GDP guidelines are in place to ensure that this quality is maintained throughout the remainder of the distribution chain. In other words, there should be no change in the quality of a product from the point that it leaves the factory to the point at which it is used by the patient, irrespective of whether the product has been sourced via a retail pharmacy or via a hospital.

The GDP guidelines require that any distribution company has a quality system in place. The general concept of quality management and quality systems is discussed in detail in Chapters 2 and 3. In the following section, the quality system will be discussed purely as it relates to pharmaceutical distribution.

5.3 Quality system

There are a number of specific requirements related to the quality system under GDP. They are reviewed below. Some of these points are returned to in more detail in later sections.

- Authorized products: products must be authorized in accordance with EU legislation. In other words, the distributor must have full confidence in the suppliers from which products are sourced.
- Storage conditions maintained: products must be kept under appropriate defined storage conditions, both during storage in the warehouse and during transport.
- Cross-contamination avoided: all possibilities of cross-contamination must be avoided, both during storage and transport. This includes not only cross-contamination between materials, but also mix-ups between different products or materials, or between different batches of the same products or materials.
- Adequate turnover of products: it is important that all products are subjected to an appropriate stock-rotation system. This will generally be FIFO, although under exceptional circumstances other systems such as last in, first out (LIFO) or FEFO might be acceptable. In any event, due consideration must be taken of expiry dates.
- Safe and secure storage: at all times, there must be protection both of the product and any people who come into contact with it. This must extend through storage into transport systems.
- Right product, right place, right time: this requirement implies that there are sufficient checks in place to ensure that the correct product is distributed and that it always goes to the correct addressee. The right time relates both to delivery performance and to the time of day that the delivery lorry arrives. (As with many of the other aspects of quality, this makes good business sense as well as fulfilling one of the requirements of the quality system.)

- Full traceability: problems with a finished product, or one of its constituent materials can be discovered at any point in the distribution chain. It is important that the traceability of all units is maintained throughout.
- Effective recall system: this is linked in with the previous point regarding traceability. Whatever the reason for the recall and wherever the ultimate blame lies, the distributor needs to be able to participate fully in any recall that might be triggered by the manufacturer or the national authority.

The way in which a distribution company complies with the requirements of GDP and sets up its quality system is covered by the remainder of the guidelines, each section of which is reviewed below.

5.4 Personnel

There is a requirement that a management representative be appointed at each distribution point, with the authority and responsibility to ensure that the quality system is implemented and maintained. The term management representative is only used in the GDP guidelines, and not in the preceding documents. However, in the Directive and the national regulations, this position is referred to as the responsible person (RP). This is the distribution equivalent of the qualified person within pharmaceutical manufacturing. The role of the RP is covered later in this chapter and that of the QP is dealt with in detail in Chapter 8. This representative should carry out the role personally; in other words, delegation is not permitted. An appropriate qualification is required. Ideally, this would be pharmacy, but this will vary with national regulations.

GDP refers to key personnel within the company having the appropriate levels of training, qualifications and experience. However, there is no statement as to which are the key personnel. In pharmaceutical manufacturing, key personnel are defined as the head of production, the head of QC and the qualified person. The heads of production and QC are required to be full-time employees, independent of one another, but having the authority to delegate their responsibilities if the size of the company requires it. In the context of distribution therefore, the key personnel can be defined as the decision-makers that have any affect on the quality of the product. This would include the head of warehousing, and the people responsible for identifying and dealing with suppliers and customers.

Personnel working within a distribution company should be fully trained both in the responsibilities of their jobs and in the general principles of GDP. Different groups of people will have different training requirements and, in some cases, there may be a need for some basic training in aspects of GMP as well. All training should be recorded, both at the organizational level (to provide information about the overall pool of resources) and at the individual level. These records are useful as an internal document, but are also a requirement for external inspections.

5.5 Documentation

Not just training records, but all documentation has both an internal and an external purpose. The authorities within any Member State have the right to view documents relating to the quality of the operation.

At the start of the chain, there needs to be a formal system of orders placed with appropriate suppliers. These suppliers can only be another authorized wholesaler, the holder of a manufacturing authorization or the holder of an importation authorization.

The requirements relating to delivery to customers is dealt with later in the GDP guidelines. However, at all parts of the chain, there is a need for accurate records. As with all pharmaceutical record making, these documents should be completed at the time that an operation is carried out and should record all significant points. Records must be easily readable and should be retained for a minimum of 5 years in an easily accessible format.

For all transactions, whether with suppliers or customers, the minimum amount of data to be recorded includes the date, the name of the product and the batch number, the quantity changing hands and the details of the third party.

All aspects of the operation that affect the quality of the product should be controlled by written procedures. Whilst procedures are a useful tool for an inspector, it should be remembered that they are principally there to control how the job is carried out. They should be written by – or at least in conjunction with – the people who carry out the job. They should be approved by an appropriate person, such as the management representative, since they form part of the quality system. Master copies should be stored carefully and only authorized copies should be in circulation. Procedures are prepared differently by all companies but, as a minimum, they should contain the name and signature of the author and the approver(s), a reference number, a review-by date and a distribution list.

A number of topics are specifically listed within the GDP guidelines as requiring procedures. These are as follows:

- Receipt and checking of deliveries: who is responsible for the process; what documentation is required; what is the quarantine procedure; and what internal labelling is required.
- Storage: location of storage and methodology; handling of quarantined materials, approved materials and rejects; and how mix-ups are to be prevented.
- Cleaning and maintenance: who is responsible for cleaning; what must be cleaned and how; the frequency of cleaning; and the recording of cleaning in a log-book.
- Pest control: the risks involved; the appropriate preventative measures; and how those measures will be recorded. (See below for a more detailed discussion of pests.)
- Recording of storage conditions: temperature and humidity recording; manufacturers' requirements for specific products, together with any national requirements; alarms and what happens if an alarm is triggered out of normal working hours. (See below for a more detailed discussion of storage conditions.)
- Security on site: who has access to storage areas; how special materials are handled; and how access can be gained out of normal working hours, in an emergency.
- Security in transit: prevention of cross-contamination; prevention of damage; and prevention of theft.
- Withdrawals from saleable stock: reasons for withdrawals, such as the provision of samples or free-gifts; who is responsible for authorizing such withdrawals; and how they will be carried out.
- Records of customer orders: as already mentioned, these will include who is the customer, what they have been supplied with, in what quantity and when.

- Returned products: circumstances in which returns are permitted and conditions to be fulfilled before materials can be returned to saleable stock. (See below for a more detailed discussion of returns.)
- Recalls: who will be responsible for co-ordination; records; and disposal of recalled materials. (See below for a more detailed discussion of recalls.)

5.6 Premises and equipment

There are no particular requirements defined in relation to construction of premises for distribution warehouses. Additionally, the equipment found in such warehouses tends to be restricted to transport mechanisms such as forklift trucks and areas with controlled conditions, such as refrigerators. Hence the requirements for premises and equipment are far less detailed than in a manufacturing environment.

The main requirement is for premises that are 'suitable and adequate to ensure proper conservation and distribution'. In terms of the physical premises, this may be interpreted as being large enough and capable of being easily kept clean and tidy.

In terms of materials of construction, companies have a fair degree of latitude. The walls of warehouses may be as simple as brick or breeze-block, painted to seal the surfaces. Flooring should also be sealed, in order to keep down the levels of dust. However, in a warehouse environment, the main consideration for the floor will be the high level of heavy traffic that it will have to bear. A suitable material is required that will not easily crack or break up. In many warehouses, there is no false ceiling fitted and the roof is exposed, whether that is painted concrete, corrugated metal or other appropriate material.

It is not usual for warehouses to have full air-conditioning systems; although in many cases, forced ventilation is provided. Air-curtains are useful at entrances to provide a positive flow of air to the outside of the building. With regard to specific conditions, such as controlled temperature or humidity, this is generally provided in smaller rooms, rather than for the entire facility.

The key aspect of the premises is that they should be large enough. The issue of product security is crucial in a building where not only many different materials or products are stored in close proximity to each other but also, in many cases, multiple batches of the same material or product will be stored together (see Section 5.12).

The areas where materials are both received into the building and dispatched onwards are very important. Ideally, there should be two loading bays: one for incoming materials and one for outgoing materials, so that there is no crossover of flows. In any event, the loading bay should be covered, so that materials are protected during loading/unloading from extremes of weather. The loading bay should be large enough for incoming batches to be kept in a reception area until the initial check on documentation has been completed.

There should also be a separate quarantine area where batches are stored whilst awaiting inspection and approval. However, if any materials have specific storage requirements, such as narcotics or products that should be stored in the fridge, these requirements should be satisfied straight away, rather than after approval.

There are a number of specific requirements in relation to the storage of pharmaceuticals that need to be achieved. First of all, they should be stored apart from

other goods. Whilst it is normal for a pharmaceutical manufacturer to concentrate on one type of product, wholesalers often store and distribute a much wider range of products. However, it is still necessary to ensure that the pharmaceuticals are stored in separate areas, with no risk of cross-contamination.

Pharmaceuticals will often have particular storage conditions that are specified by the manufacturer. These will relate to such parameters as humidity, temperature or light. The distributor must ensure that all requirements are understood and that appropriate controlled areas are available.

The temperature of the warehouse should be monitored on an ongoing basis and recorded regularly, even in the areas where temperature is not controlled. Many companies adopt the procedure of recording at least twice in every 24 hours. Others use a maximum and minimum thermometer. In either case, the records should be reviewed occasionally, so that the overall profile of storage conditions within the warehouse are known.

For areas where conditions are strictly controlled, such as refrigerators or low humidity rooms, there should be recorders that are attached to alarms, so that any problems are dealt with immediately. Controls in these areas should be sufficient to ensure that all parts of the area are maintained within the required conditions. Consideration should be given to what happens if the alarm is triggered outside working hours. Will a failure of a fridge that takes place at 19:00 on a Saturday evening have to wait until 09:00 on a Monday morning before it is observed and rectified?

A distribution company will tend to be more susceptible to pests than a manufacturing company. The location is often less well controlled and the loading bay doors are open for much of the time. In many cases, the company will have neighbours whose businesses encourage pests, such as food-processing premises.

In this context, pests can be defined as any unwanted animals, from stray dogs or cats, through rats and mice to insects. There need to be measures in place for prevention and control, and these measures need to be recorded.

As previously mentioned, the company needs to have an appropriate stock rotation system, which will generally be FIFO. Regular checks should be made on physical stock to ensure that this system is operating effectively.

Owing to the high number of stock-keeping units found in an average wholesaling company, the level of computerization in the distribution industry is generally as high, if not higher than that found in manufacturing companies. However, whether the system is computerized or manual, it is important that there is a flagging mechanism to highlight when a particular batch of product is about to reach its expiry date. There is no problem with the company offering special deals to its customers in order to increase the speed of sales; however, once the expiry date has been reached, the batch must be removed from stock. (Since the distributor's customers will also be bound by the same expiry dates, the success of any such 'sale' is likely to be in question unless it is held sufficiently far in advance.) Any expired stock must be segregated from saleable material, and cannot be sold or otherwise supplied for use.

Damaged stock can come in a number of different forms. It may be that the packaging is spoilt or that tamper-evident seals are broken, even if the bottle or pack is not itself destroyed. In any case, where there is a possibility of contamination of the product, it must be removed from stock. It must be completely segregated, to prevent any possibility of accidental sale or contamination of other product.

A safe mechanism for destruction is required, both for damaged and expired stock. Such destruction should be fully recorded.

The requirement of appropriate premises and equipment extends to the requirement that proper conditions are maintained during transport. This means in particular that the condition of the vehicle should be well maintained. This is relatively easy for a distributor to control when the company has its own fleet of lorries. However, it may be harder to manage when the company is renting its vehicle or contracting out the transport elements of the business.

5.7 Deliveries to customers

In the same way that purchases can only be made from authorized persons, sales to customers can only be made to authorized persons. This means that a sale can only be effected with another wholesaler or with someone who is authorized to supply pharmaceuticals to the public.

Any sales must be accompanied by documentation that includes the date of the transaction; the name and dosage form of the pharmaceutical; the batch number; the quantity sold; and the name and address of both parties to the transaction.

A distributor is considered to be under a public service obligation, which means that, in any emergency, they must be in a position to maintain their regular supply to their customers. Hence they are bound by much more than the normal rules of good business to ensure that they always have required products in stock.

As part of the requirements relating to deliveries to customers, there are a few aspects concerning transport conditions to be complied with. Firstly, product identification should be maintained. This means that, for large consignments, different batches of the same material should not be mixed. When the delivery is made up of individual units, the batch number is easy to check, but such units should be properly packed to ensure they do not go astray.

Secondly, there should be no cross-contamination allowed. This cross-contamination could be in either direction: contamination of the product itself or, depending on its nature and active ingredients, contamination by the product. Cross-contamination should be avoided with other medicines, other materials and with people.

Thirdly, precautions should be taken to avoid damage to the delivery; such damage could include spillage, breakages or even theft. Finally, all storage conditions should be maintained and the deliveries should be protected from the ingress of pests.

5.8 Returns

There are two types of returns that a distributor must deal with. These are discussed separately below.

Returns of non-defective products

Depending on the terms of agreements between distributors and their customers, there may be occasions when non-defective products are returned to the warehouse. Such

material should be segregated from saleable material, pending a decision on how it should be treated.

There are only three possible routes for returned material. It can be reapproved and put back into stock for sale; it can be returned to the manufacturer; or it can be destroyed.

Before material can be returned to stock, it must undergo some rigorous checks. First of all, it must be in the original, unopened containers and must all be in a good condition. The history of handling and storage of the material since it originally left the distributor's premises must be known with certainty. There must be an acceptable shelf life remaining.

Assuming the returns satisfy all the above conditions, they must be examined and assessed by QC as though it was a new delivery. Considerations would include the nature of the product, any special conditions that the product is subject to and the length of time that has elapsed since the product was sold. If in doubt, advice should be sought from the original supplier or manufacturer.

If the returns are judged to be suitable for resale, they are formally released back into stock and entered into the FIFO system at an appropriate point. Full records must be kept of this process.

Returns of defective products

The topic of recalls is dealt with fully in Chapter 4. However, there are a few specific points to be noted in relation to recalls within distribution. There is a distinction made between urgent recalls, for which an emergency plan is required, and non-urgent recalls, which can be managed via a recall procedure. However, in either case, there must be a responsible person appointed to co-ordinate the activities.

Distributors will always be involved in recalls, and on occasion, it will be a distributor who will discover the problem that leads to a manufacturer triggering a recall. However, it is rare for the distributor to be the cause of a recall. They will generally be merely a part of the chain. Depending on the reason for the recall and its severity, a decision will be taken by the manufacturer as to whether the recall will take place at wholesale level, or whether it will extend to the retail sector. In this case, it is critical that the distributor can easily access the records kept of all deliveries of the batch of product in question.

5.9 Self-inspections

The topic of self-inspections is covered fully in Chapter 11. At this point, it is sufficient to state that a distributor should have a written self-inspection programme with full records of observations and recommendations, just as much as there is a requirement for a manufacturer to have such a programme.

5.10 Provision of information to Member States

Distributors wishing to operate in Member States of the EU other than the one in which the original authorization has been issued are required to notify the appropriate authorities in the new country, in order to determine whether any additional public service obligation exists.

5.11 The role of the responsible person

Within the EU, the role of the RP is defined within an organization that carries out the wholesale distribution of medicinal products. This is the equivalent of the QP within manufacturing.

5.11.1 Statutory basis for the responsible person

The role of the RP was established within the EU in the 1992 Directive on distribution of medicinal products. It was subsequently enshrined in the national laws of the various Member States.

The RP is nominated by the company, and approved by the licensing authority. At this point, they can be named on the wholesale dealer's licence.

5.11.2 Eligibility to be a responsible person

It is not a stated requirement that, in order to be an RP, someone must be a pharmacist or eligible to carry out the role of a QP. However, it is a requirement that the RP must have appropriate knowledge and experience.

The knowledge includes the EU requirements and appropriate national regulations, a working knowledge of GDP and details of the licence for which the nomination is made. This would include the details of the products involved and their storage requirements, together with the full distribution supply chain, from sources of product to customers.

In terms of experience, it is a requirement that an RP has at least one year's experience either in the practical aspects of procurement, storage or sales plus an additional one year in a managerial role.

In small companies, the licence holder may be permitted to be the RP, but this is not ideal. The RP does not have to be an employee to the company. As with QPs, there is a possibility of a self-employed contractor fulfilling the role.

5.11.3 The duties of the responsible person

The role of the RP is to ensure that all the requirements of the licence, and the appropriate regulations and guidelines are carried out. It is designed to prevent problems arising through the use of inappropriate sources of product, inadequate storage and distribution procedures, or sales to unauthorized persons.

In order to carry out the role of the RP successfully, there are a number of requirements that need to be fulfilled.

- The RP should report directly to the licence holder or to the managing director of the company.
- Full access should be provided to all facilities and records.

- All facilities should be audited on a regular basis to ensure that everything is satisfactory. In a situation where these duties have been delegated, the RP should personally check each procedure on at least an annual basis.
- Records of all monitoring and control activities should be maintained.

5.11.4 The responsible person and the management representative

If a wholesaler's operations extend to more than one site, it will often be impossible for the RP to carry out all their duties on a day-to-day basis, particularly if the operations extend across the whole country. In this case, it is permissible for the company to appoint deputies who will act as delegates. In the GDP guidelines, this role is referred to as the management representative.

5.12 Case study

Companies that deal only with other wholesalers or with larger customers have the opportunity to sell product in whole cases only. This makes the product security issues slightly easier to deal with.

However, when a company deals with smaller companies, such as individual retail pharmacies, orders will frequently include quantities of product of less than a whole case. In these circumstances, the company will be left with open cases on their shelves. This means that there will be a mix of sealed and open cases being stored together and it may be possible to find individual sales packs being stored on open shelves. This is not only a nightmare from the point of view of stocktaking, but increases the security risks within the warehouse.

One solution to this problem is to decouple the storage of sealed and open cases. All sealed cases are stored in the main warehouse and orders for multiple cases are serviced from here. However, smaller storage spaces, using pigeon-holes or plastic boxes, are used for open cases. Orders for smaller quantities are serviced from this area. This ensures that different storage conditions can be provided for the different circumstances and product security is thus reinforced.

6

The management of quality

6.1 Introduction

Each holder of a manufacturing licence should have a quality control department. This means that the quality control department must have people that are clearly responsible for all quality control activities. They must also have access to suitable facilities to perform all the testing that is required.

The independence of quality control from production is considered fundamental. This means that the quality control manager should not report to the production manager. Likewise, the production manager should not report to the quality control manager. Legislation in different countries deals with this issue in different ways.

It is no good assigning an individual with responsibility for quality control if that person does not have sufficient resources to carry out their responsibilities. Adequate resources should include:

- sufficient numbers of trained and experienced staff; and
- an appropriately designed laboratory, suitably equipped to enable all the quality control functions to be carried out in accordance with specifications.

Ideally, the head of the quality control department reports directly to the president of the company. This means that, for the key decisions on product quality, there is no interference from manufacturing staff. An alternative to this, which might in some circumstances be preferable, is that the quality controller reports to a professionally qualified technical director. This person is also responsible for production activities.

This position does rely on the professionalism of the jobholder. The advantage of having the quality controller reporting to a professionally qualified person is that it encourages a scientific and professional review of the product quality against the standards and the products use. This scientific evaluation of the product may not be possible with a chief executive who has no scientific background.

6.2 Evolution of quality management

The development of the quality management function within a company tends to be an evolutionary process. For most companies in Europe and the USA, this is a process that started in the early 1970s or even earlier, and is now in the late stages of maturity. However, there are still companies in some parts of the world that are in the early stages.

6.2.1 Laboratory function

In the first stage, there is only a laboratory function. All countries, no matter what the stage of maturity their industry has reached, have a registration process for pharmaceuticals, which issues licences before a product is launched on to the market. This implies that there will always be a requirement for some analysis of raw materials, intermediates and finished products.

The position of the laboratory within the company at this point tends to be as a service to production. Often, it is reporting in to the production manager. In some cases, there is no laboratory within the company itself and the process is subcontracted out, either to a government organization or to a private company.

Within the company hierarchy, the laboratory personnel do not have the same status as the production personnel. The concept of independence of QC from production does not exist. Responsibility for releasing the product remains with production. Worrying as it may seem, this situation still exists in some companies in places like Russia and the CIS countries, where the national enforcement of GMP requirements is not yet established.

6.2.2 Subordinated QC function

The next stage tends to be the widening of the role of the laboratory to cover other testing requirements, such as environmental monitoring. At this point, the company may be said to have a QC function. The responsibility for product release tends to move at this point to the head of QC. There are still occasions, however, where this function is subordinated to production.

The process of document audit, however, does not form part of the release process. Process records exist, but often they are in log-books that remain at the point of production, rather than being gathered together into a batch dossier. From experience, the view of both production and QC personnel at this point can be ‘QC are responsible for physical testing only. The documentation belongs to, and is the business of production’.

6.2.3 Independent QC function

At the next stage, there is a realization of the need to separate the responsibilities of QC and production. The QC function no longer reports to the head of production. Where it is located within the organization varies from company to company. In some companies, it

reports in to the development department, if such a function exists. In other companies, it reports in to a technical director, along with, but not necessarily at the same level as, the production department(s). The process of document audit may be added to its responsibilities, but this is not necessarily the case.

At the next stage, the importance of QC relative to production is recognized and the head of production and the head of QC tend to reach a point of equilibrium within the organization.

6.2.4 Introduction of quality assurance

The next stage is where the function of QA first appears within an organization. This is often the point where a company makes huge steps forward towards the achievement of GMP compliance. QA tends to start off with responsibility for such topics as validation, document audit and GMP training. Often, responsibility is given to a single person to set up the function and the main problem is how to cover such a huge range of responsibilities on their own.

During GMP audits, one of the questions that many companies at this stage in their development ask is: 'where should QA be located in the organization?'. At this point, there is often no direct relationship between QA and QC. The latter, wherever it is situated in the organization chart, is still seen as providing a service to production. On the other hand, QA is seen as a staff function. Frequently, it reports in to the general manager or senior technical person within the organization.

As the organization matures, the role of QA grows and the number of personnel working within the department increases. However, there are still a number of different organizational models that are adopted by companies.

6.2.5 Alternative models for quality management

In some companies, QA evolves into quality management and QC becomes absorbed as one of the departments. At this point, the laboratory function may remain as part of QC or it may revert to being a pure service centre for production. Conversely, there are companies in which QA becomes one of the departments of QC, alongside the laboratories.

In other companies, QC and QA remain as separate functions with a complete separation of responsibilities. Document audit may at this point be the responsibility of either department. The QPs or authorized persons with responsibility for batch release do not have a fixed position in all of this and their location within the organizational structure is also variable.

6.2.6 Quality management in a multinational company/corporation

The evolution and possible models described above are seen in companies with single sites or in much larger organizations. However, there is a further aspect that is seen

within the multinational companies/corporations (MNCs) – the corporate quality function.

The MNC has a number of factories around the world, producing product. Some of those factories will be wholly owned subsidiaries, some will be joint ventures with local companies and some will be contract manufacturers. Each of these factories will have their own quality management system, covering QC and QA. However, there is frequently a corporate function as well, which operates from head office. This department will cover such functions as development of company-wide quality and procedures, auditing of individual factories and approval of contractors.

6.3 The role of the quality manager

Chapter 2 covers the requirements that must be fulfilled in order to ensure that a company has an effective quality management system. Who actually carries out the various activities will vary from company to company. However, this chapter looks at the topic from a different angle and discusses the role of the quality manager within a company. The role can be looked at from two viewpoints: the technical one or the business one.

6.3.1 Technical responsibilities of the quality manager

Starting with the technical aspects, the quality manager is firstly responsible for the approval or rejection of all starting and packaging materials, and all intermediate, bulk and finished products. This is a critical area where independence is paramount.

Secondly, the quality manager is responsible for the evaluation of batch records coming from production. This should be done as part of the product release process. The purpose is to be reassured that everything has been produced in accordance with the agreed process and meets specifications. If there have been any deviations from the agreed process, these need to have been authorized by responsible persons.

The quality manager is also responsible for ensuring that all the required testing is completed in accordance with specifications and for approving all the instructions that are required for the organization and implementation of testing. However, the development of all these instructions, policies and procedures may well be done in co-operation with production and development personnel.

The quality manager is responsible not only for in-house analysis, but also for all testing carried out on contract. There must be certainty that the contract acceptor can conduct the testing to the required standard, has all the necessary personnel, has the necessary equipment to conduct the testing and has a written contract specifying the responsibilities of all parties to the agreement.

The quality manager is responsible for ensuring that all the facilities and equipment that are under their control are properly maintained. Validation of analytical methods and calibration of laboratory equipment must be carried out. This ensures that the results achieved by following the validated processes can be relied upon to indicate the correct result. However, some aspects of validation will almost inevitably be shared with production and engineering.

Finally, the quality manager is responsible for ensuring that the people who carry out all this work are well trained and motivated at the commencement of their work and that they receive regular training and retraining.

6.3.2 Shared technical responsibilities of the quality manager

There are a number of responsibilities that the quality manager will share with the equivalent person within production. In order to ensure that nothing is missed and that there is no duplication, it is important that both positions have clear written job descriptions, showing where the shared responsibilities are.

Approval of all procedures and documents used in manufacturing is a shared responsibility. There is also a requirement to ensure that an effective system of change control is implemented and that, as documents are updated, all those who use them are given the latest version.

Monitoring of the manufacturing environment is a task to be shared between QA/QC, production and engineering. They should conduct the monitoring and testing as appropriate, with the results available to all who need to know them.

Both quality and production have a role to play in the development and maintenance of an appropriate factory sanitation and hygiene management system. Similarly, both have a major contribution to make in the validation of processes and the calibration of equipment.

Just as a comprehensive organization chart is required for a factory, so a comprehensive training programme is required for all its personnel. Both production and quality control have a role to play in the development of that training programme, and they also have a shared responsibility for its implementation.

Approval of all suppliers and contract manufacturers is also an area of shared responsibility, with each contributing their own particular expertise. The specification and monitoring of storage conditions will also be shared, but with the additional involvement of the development function.

Since both quality and production functions are responsible for the generation of records relevant to batches, then the arrangements for the storage of those records may be a shared responsibility. Alternatively, a separate department may be available that manages all aspects of documentation and batch records. (This will generally be decided by such peripheral issues as where there is extra storage space available.)

Monitoring of compliance with GMP is very much a shared responsibility. This emphasizes the fact that the achievement of GMP is everyone's responsibility.

Some aspects of sampling may be conducted by people other than QC. If sampling is to be done by people other than QC, then there must be a clear definition of who is taking what sort of sample and when, so that there is confidence that what is being done is appropriate. Sampling should only be done by persons trained in the methods to be used.

6.3.3 Business role of the quality manager

The quality manager may be independent of production in terms of the technical functions of the position. However, additionally, the quality manager is part of the management

team that runs the organization and, as such, has a responsibility to ensure that the business is not adversely affected by any of the activities of quality management. Goldberger (1991) discusses the five elements of a business that quality management must affect positively. These are cost, regulatory aspects, quality, staff motivation and operational viability/flexibility. If any of these elements is negatively affected, then the quality manager is not operating effectively.

In order to achieve these objectives, it is necessary for the quality manager to deal effectively with people at many different points within the organization. Apart from the obvious interface points, such as production, engineering and warehousing, there are others, such as purchasing and marketing. Goldberger (1991) presents a useful checklist of these relationships and what they would entail.

6.4 The quality management system

The topic of quality management systems in the formal sense of the word is fully covered in Chapter 3 in the discussion on ISO 9000. There are a small number of examples of such registrations within the pharmaceutical industry. In particular, some of the regulatory authorities have been leading the way. For example, in the UK, the Medicines Control Agency is registered to ISO 9002.

There is a useful PIC/S document (PI 002 – 1) that reviews the topic of quality systems. Whilst it is written primarily for pharmaceutical inspectorates, it can be used as a reference tool in its own right. It defines a quality system as 'the sum of all that is necessary to implement an organization's quality policy and meet quality objectives. It includes organization structure, responsibilities, procedures, systems, processes and resources'.

The principal documentation of a quality system is contained in a quality manual and quality procedures. The quality manual is the document that describes how the organization addresses the various clauses within the quality standard. It will include reference to the quality procedures that describe the activities of the organization and the ways in which the quality system is to be maintained.

The PIC/S document contains sections on organizational structure, documentation and change control plus other quality system requirements such as records, procedures, internal audit, and corrective and preventive action. After the initial recommendation document, there is an annex specific to documentation of a quality system. This contains sample text. Once again, it relates specifically to inspectorates, but could be adapted fairly easily for use by other types of organization.

6.5 Summary

This chapter deals with the management of quality. It discusses the process by which a quality management function evolves, and emphasizes that companies across the industry are at different levels of evolution at any one point in time.

Most companies within the developed world are at a high level of maturity with respect to the organization of the quality management function. However, it is by no means a fixed situation. As with so much of pharmaceutical manufacturing and GMP compliance, there are no right answers – only the right answer for a particular organization. There are frequent changes still, as companies seek the best way to organize quality within their own organization.

7

The cost of quality

7.1 Introduction

Anyone who works in a manufacturing environment, whether with responsibility for production, QC, engineering or process development will recognize the scenario of having to be a juggler. All the time we are at work, we are trying to reconcile and satisfy the needs of a variety of people – all of whom will have apparently different goals. On the one hand, there are the increasing pressures on costs coming from the finance department, and often from the boardroom. On the other hand, there are ever increasing technical and validation requirements coming from the regulatory authorities. Finally, the commercial people don't really care how much validation is done, so long as the product gets to the marketplace as quickly as possible.

In this position, the pharmaceutical manufacturing personnel are faced with an apparently irreconcilable set of objectives to achieve. The purpose of this chapter is to discuss an alternative way of thinking that can help to achieve all the objectives in one go.

The cost of quality is a useful tool that has been used in a variety of industries to look at costs in a new way. It was first developed by Joseph Juran, who talked about 'the cost of poor quality'. It is the tool that led Phillip Crosby to declare in the 1980s that 'quality is free'. (For a full discussion on Juran and Crosbys' views on quality, see Chapter 14.) It can be used to justify expenditure on quality measures, including validation.

The chapter begins with a discussion of the definition of the cost of quality. It then moves on to review how quality costs can be measured. Finally, there are a number of case studies of applications of the cost of quality within the pharmaceutical industry.

7.2 Definitions of cost of quality

Cost of quality is a tool that has been used in many industries, usually within a total quality management or performance improvement programme. There are three main types

of quality costs: failure costs; appraisal costs; and prevention costs. The first of these is sometimes classified as non-conformance costs, whilst the latter two are classified as conformance costs.

7.2.1 Failure costs

Failure costs (also known as the costs of non-quality) are those associated with getting things wrong. They can be tangible costs, such as the cost of rejects or reworks, or they can be intangible costs, such as lost sales, damage to image or problems with the regulatory authorities.

A prime example of failure costs, covering several of these categories occurred in India some years ago. At least one multinational company had failed to validate their method for destruction of waste packaging materials. A pirate company retrieved some waste material from the disposal area and used it to package and sell counterfeit material. When the regulatory authorities found out what was happening, the multinational was shut down for ten days, resulting in failure costs in all these categories.

7.2.2 Appraisal costs

Appraisal costs are those associated with checking that things were done correctly. It should be emphasized that this is not a value-adding activity of itself; it is merely an historical measurement of what has already happened.

Examples of appraisal costs are raw material testing, in-process controls and finished product testing. It could also be said that inspection costs, such as the fee for a visit from the regulatory authorities come under the category of appraisal costs.

7.2.3 Prevention costs

Prevention costs are the costs associated with making sure that things will be done right. This is the one activity of the three that can be considered to be value adding. Examples of prevention costs are all areas of training; audits carried out by the company – whether internal self-inspections or supplier audits; and validation.

It is necessary at this point to return to the problems in India, referred to under failure costs. The knock-on effect of the incident was that the FDA visited other multinationals in India and scrutinized very closely their validated systems for waste disposal. Companies that had already invested in the systems were able to demonstrate that they were in compliance.

7.3 Using the cost of quality tool

Having defined the three types of costs, consideration needs to be given to how the tool is used. All the activities related to quality are measured and categorized as failure, appraisal or prevention costs. By highlighting the various costs in this way, it makes it

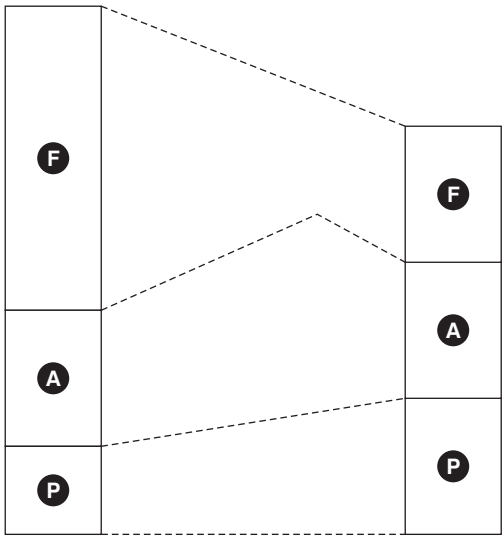

Figure 7.1 The cost of quality. F = failure, A = appraisal, P = prevention.

easy to decide where to focus efforts in order to improve performance and also reduce costs.

Studies of quality costs across many different countries have led to an average of between 15 and 30 per cent of total sales. Of this, it is estimated that up to 75 per cent will be accounted for by failure costs.

Figure 7.1 shows what happens when a company starts to use cost of quality as a tool.

The column on the left represents the typical situation in a company that is not controlling its quality costs. The central portion represents the way that the tool is used. Particularly in the pharmaceutical industry, this may be accompanied initially by a rise in appraisal costs, since it is necessary to ensure that any changes made have not been detrimental. However, in the longer term, the appraisal costs can be reduced. For example, by instituting a supplier audit system (increasing the prevention costs), it should be possible in the medium to long term to reduce or eliminate raw material testing (reducing the appraisal costs).

However, the more important result is the effect on failure costs, which can be reduced significantly. In the example above, the overall effect of implementing a supplier audit system should be to reduce problem with deliveries, improve the quality of the specification and reduce the level of waste produced when the material is processed (reducing failure costs). This is why Philip Crosby said that quality is free.

There are a variety of ways in which a cost of quality measurement can be used within a company. First and foremost, it can be used as a communication tool to make people aware of costing issues and thereby influence company strategy.

Cost of quality measurements can be part of the decision-making process, as an adjunct to discounted cash flow or sensitivity analyses for project evaluation. They can also be used to monitor performance across an organization, in order to identify

priorities for improvement and to set cost-reduction targets. Once the activities are being carried out, cost of quality can be used to check progress towards target. It can also be used to carry out a cost–benefit analysis against specific quality-related activities such as TQM programmes or ISO 9000 certification. Benchmarking can be carried out across different parts of an organization or between companies in the same or similar industries.

Finally, cost of quality measurements can be used in the development of budgets and product costing. In this context, it can be a complementary tool to activity-based costing.

The cost of quality tool can be used as a one-off measurement to provide information about a specific activity or it can be used on a continuous basis as part of the normal performance monitoring of the company. It is most effective in the latter case, if the measurement is presented as one of the regular indices in the management accounts.

7.4 Establishing a system for calculation of costs of quality

There are a number of reference sources for methodology relating to the measurement and calculation of quality costs. Two of these are referred to below.

7.4.1 British Standards

Since the early 1980s, there has been a document published by the British Standards Institute relating to quality costing. The latest editions were published between 1990 and 1992. BS 6143–2 was issued in 1990 and deals with the traditional method of determining prevention, appraisal and failure costs. BS 6143–1 was updated in 1992 and presents a process costing model, which can be applied to a wide range of businesses.

7.4.2 Tefen methodology

Malchi and McGurk (2001) present a methodology for measuring the cost of quality. Instead of the traditional cost of quality definitions of prevention, appraisal and failure costs, they use the terms operating costs and non-conformance costs. This paper provides details on how such a measurement system might be implemented.

7.4.3 A simple approach to the cost of quality

The following methodology has been used by the author in unpublished studies of the cost of quality within the pharmaceutical industry. It consists of a number of steps, which are described in Table 7.1 with examples.

Table 7.1 Stages in a Cost of Quality Project

Stage	Example
Establishment of a project team, encompassing the departments in the company involved in the process under discussion	QA officer – team leader TQM manager – facilitator Manufacturing supervisor Purchasing operative Warehouse manager Packaging operative
Identification of the scope of the project	Entire product pipeline for product X from raw material purchasing through manufacturing and packaging to release for sale
Identification of stages in the product pipelines	Purchase of raw materials QC approval of raw materials Manufacture of bulk product QC approval of bulk product Packaging of finished product QC release of finished product
Identification of key steps in each stage	Manufacture of bulk product Engineering set up Routine maintenance Training Storage of raw materials Manufacturing Reject material Sampling and testing Approval for packing
Grouping of steps into Cost of Quality categories	Basic processes Manufacturing Prevention costs Training Appraisal costs Sampling and testing Failure costs Reject material
Assignment of units of measure for each step	Training: person-hours Sampling and testing: person-hours and cost of material Reject material: cost of material
Measurement and estimation of the activity associated with each step	Sampling and testing: × person-hours; a kg
Identification of costs	Sampling and testing: × person-hours at £y per hour; a kg at £b per kg
Analysis and interpretation of results	Total sales = S Total quality costs = T Percentage Cost of Quality = T/S × 100
Derivation of useful information	Main source of reject material is machine M in process step 3. This would be a priority area for investigation

7.4.4 Prerequisites for successful establishment

Many programmes related to quality improvement activities have been set up within companies over the past three decades and many of them have not been successful, owing to an inappropriate culture or the failure to comply with prerequisites for success. This topic is more fully discussed in Chapter 15. However, this section deals with the issues that need to be anticipated and dealt with in the context of cost of quality.

One of the biggest barriers to a successful measurement could be the mismatch between the company's current financial monitoring system and the items that need to be measured in order to calculate the cost of quality. In order to prevent this barrier from arising, it is important to involve the finance department from the outset.

Any activity that, of necessity, focuses on problems with the way that people carry out their jobs can be seen as a process of criticism and blame if not presented correctly. It is important that the individuals concerned fully understand that the process is not personally based and can be beneficial to them in the long term.

A cost of quality project will tend to be time consuming over at least the initial stages. Inevitably, the members of the team will have other 'real' jobs that they will have to continue to carry out in parallel. It is important that sufficient resources are provided to ensure that team members are not overwhelmed with conflicting priorities.

One of the main ways of ensuring that these barriers will not arise is to provide ongoing, very visible project championship from a senior manager (preferably a board member). The support of such a person will disseminate the message that the company is serious about this activity and is not going to let it slip quietly into oblivion after a respectable interval of time.

Apart from the project champion, there must also be a project manager who will run the activity. This person will need to meet with the senior management team to determine who are the most appropriate team members. These people will come from a variety of parts of the company and will be chosen for various reasons: obviously there need to be people who understand the process and can explain the detailed steps. However, it is also important to have people who are creative in their thinking and are willing to consider doing things in a different way. These people can also be useful in presenting a 'fresh pair of eyes' to the process. Sometimes, the process experts are too close to the detail to be able to see things clearly.

Once the team has been chosen, the project manager will need to establish the requirements in terms of time. This should be agreed with the members' managers so that members do not have problems in attending meetings or carrying out allocated tasks in between.

Finally, the team should meet to agree its objectives and *modus operandi.* Depending on how large the company is and how well the members know each other (or not, as the case may be), it could be beneficial to have some sort of ice-breaker or other team-building exercise at the start to ensure that the team operates effectively and efficiently during the course of the project.

The project manager should ensure that appropriate communication mechanisms are established, so that the project champion and other senior managers are aware of what is happening.

7.5 Case studies

There are not too many published examples of cost of quality exercises that have been carried out within the pharmaceutical industry. This section presents a published example from another industry that can be considered to have similar characteristics to pharmaceuticals and a recently published case from within our industry. Additionally, it describes some case studies from within the industry that have not been published.

7.5.1 British Aerospace (Dynamics) Ltd

This company grew out of the Air Weapons Division of British Aerospace and was established in 1989. The parallels with the pharmaceutical industry lie in the lengthy and very expensive research and development phases that both industries have.

The company has been measuring its quality costs since the mid-1980s, using an adaptation of the methodology presented in BS6143. The tool was seen from the start as an integral part of the total quality management programme.

In 1989, following pilot studies on two manufacturing sites, a full-scale analysis was carried out of the cost of quality across all five manufacturing sites. It was found that 11 per cent of total production costs could be identified as quality costs. Of these, 22 per cent were classified as prevention costs, 30 per cent were classified as appraisal costs and 48 per cent were classified as failure costs. These findings and the associated priorities that they identified were then used to target improvement activities in order to reduce costs drastically.

This case study is quoted with kind permission of Dr Barrie Dale, Manchester School of Management, UMIST, UK.

7.5.2 Pharmaceutical manufacturing

Malchi and McGurk (2001) quote the case of a pharmaceutical company that has used the Tefen methodology to implement a cost of quality programme that managed to measure more than 80 per cent of the quality costs. A high-level steering committee reviewed the measured indicators on a monthly basis and prioritized cost reduction activities based on the findings.

As a result of this programme, the cost of quality has been reduced by 11 per cent, by the use of quality groups within production, QC discrepancy re-engineering and QC resource modelling.

7.5.3 Diagnostic product manufacture

A company producing a variety of diagnostic kits carried out a one-off exercise to measure their cost of quality as a starting point for a programme of continuous improvement.

They found that the overall cost of quality equated to 12 per cent of sales value (against a reported level of 15–30 per cent across other industries that had employed the tool). Of this, 19 per cent were classified as prevention costs, 20 per cent were classified as

appraisal costs and 61 per cent were classified as failure costs. Further analysis of the latter showed a split of 54 per cent internal failure costs against 7 per cent external failure costs.

On reflection, it was concluded that the lower than expected figure for cost of quality against sales was due to the fact that the pharmaceutical and related industries are already heavily regulated with respect to quality requirements. This was supported by the fact that most failure costs were internal; problems that did occur were being identified before the products were released on to the marketplace.

7.5.4 Primary and secondary manufacturing of pharmaceuticals

A multinational company decided to carry out a one-off exercise to evaluate the appropriateness of the cost of quality methodology within their organization and to determine the principal conformance and non-conformance costs for a major product line.

The entire manufacturing pipeline was studied, from purchasing of raw materials, through production, quality and engineering processes, to customer order management and dispatch of finished product. The process was determined to contain several hundred activities, of which 75 per cent were found to be adding cost but not value to the product.

The overall cost of quality was found to represent 19 per cent of the cost of manufacture. Of this, 85 per cent was due to failure costs, 5 per cent to appraisal costs and 10 per cent to prevention costs. Further analysis of the failure costs revealed that over 90 per cent of the failure costs could be attributed to lost yield, rejects, storage-related costs and equipment breakdown.

The exercise was considered to be a success from the point of view of identifying priority areas for improvement activities. In effect, it confirmed the suspicions that senior management already had about the main problem areas. However, it had the additional benefit of quantifying the problems. This was achieved despite the fact that the traditional measurement systems in place did not lend themselves to this methodology and that specific data-collection exercises had to be initiated in many cases.

From the point of view of assessing the methodology for further use, it was concluded that widening the use across the whole organization would be impractical at that point in time. Despite increasing pressure to improve productivity by controlling costs and recognition of the importance of quantifying failure costs, there were a number of barriers that were identified.

These barriers included familiarity with and faith in the established systems of cost control, a reluctance to change the status quo (coupled as always with a fear of change) and pressure of work. This confirmed the fact, discussed above, that this sort of tool will only be effective if set up correctly within the right company context and culture.

7.6 Summary

This chapter reviews one specific quality management tool – the measurement of cost of quality. It discusses the origin of the tool and common definitions. A number of models are referenced for establishment of a monitoring programme.

There are relatively few published examples of cost of quality projects carried out within the pharmaceutical industry. However, unpublished data suggest that quality costs within this industry would tend to be somewhat lower than in other industries, owing to the high level of regulation that is already in place with regard to quality. Notwithstanding that fact, it would appear that use of the tool could be beneficial within a pharmaceutical company. However, in order for it to succeed, it is important that the right culture is in place and that the cost of quality measurement (whether a one-off project or an ongoing programme) has the support of a high-profile project champion.

8

The qualified person

8.1 Introduction

The term 'qualified person' is universally recognized in Europe, although not always used in practice. For example, in France, the role is called the *pharmacien responsable* (RP). In other parts of the world, other terms, such as 'authorized person' or 'responsible person' are more frequently used. However, whatever the precise terminology used, each company responsible for supplying pharmaceuticals needs to appoint one or more people whose responsibility it is to release batches of product on to the marketplace. From a broader point of view, the role of such a person is to ensure that the final user of any drug, the patient, can be sure that that drug meets all the requirements of safety, quality and efficacy. It is the final act of quality assurance by the company.

It is not only the terminology that varies around the world. The degree of development of the system for appointing and controlling such people is also variable. The system within the EU has been developing over the past 25 years, and is evolving still. Yet, even here, there are significant differences in interpretation and approach. Davies (2001) presents a good overview of the situation in Europe.

This chapter begins with a detailed description of the EU system, from the directives issued in 1975, through the training and registration of qualified persons, to the actual facets of the role. Next there is a section discussing how the role is covered in the USA. Finally, there is a brief review of the situation in a number of other parts of the world.

8.2 The qualified person in the European Union

Any company that manufactures pharmaceuticals in the EU, or imports pharmaceuticals into the EU must appoint a QP, who will be named on the manufacturing or importation licence, respectively. The licensing authority has the right to accept or reject the nominated individual.

8.2.1 The EU Directives

The requirement for a company to appoint a QP first appeared in the 1975 EU Directive 75/319/EEC, which was subsequently amended in 1985 and 1993. It covers the duties of the QP, the conditions that must be satisfied if a person is to be considered eligible to be appointed as a QP and the necessity for each Member State to ensure that the requirements are controlled, by means of such measures as a code of practice.

As a result of these directives, the requirements are then included in the national legislation. In some cases, additional literature is then issued by the national licensing authority to describe the required procedures. (As an example of this cascade of documents, see the references to the UK regulations and explanatory leaflets in the Bibliography.)

8.2.2 QP eligibility

The EU Directive states that to be a QP, a person must have appropriate knowledge and industrial experience. The original discipline of that person may be as a pharmacist, a chemist, a biologist, a doctor or a veterinary doctor. However, the application of this varies within the Member States.

Within the UK, Republic of Ireland and the Scandinavian countries, all disciplines are accepted. This may be in part a reflection of the fact that the number of industrial pharmacists is relatively low. A similar situation also exists in Spain.

In Holland, there is a preference for pharmacists, although QPs who qualify under the UK system will be accepted. In France, there is an absolute requirement for the RP to be a pharmacist. In Germany, two pharmacists are involved in the process of batch release: one with responsibility for production and the other with responsibility for quality control.

8.2.3 QP disciplinary action

As mentioned above, the EU Directive requires that the performance of the duties of QP be subject to some manner of control. One option is to operate according to a code of practice. Such a code was developed and published in 1993 by three professional bodies in the UK: the Institute of Biology, the Royal Pharmaceutical Society of Great Britain, and the Royal Society of Chemistry, in discussion with the Medicines Control Agency.

It was updated and issued as Version 2 in February 2000. The text of this code of practice can be downloaded from the websites of any of the three professional bodies (details given in the Bibliography). In general, the differences between Versions 1 and 2 are more to do with wording than content. The terms ‘product licence’ and ‘manufacturer’s licence’, which apply in the UK, are replaced, respectively, by ‘marketing authorization’ and ‘manufacturing authorization’, which apply across the EU. There are additional paragraphs detailing the requirements in relation to imported

products and a completely new section dealing with the situation where a QP is not a direct employee of the company, but is contracted to carry out the role on behalf of a company (see Section 8.2.9). The section on education and training has been revised under the heading of continuous professional development (CPD) and statements by each of the professional bodies regarding their stance on CPD are included as a completely new Annex 1 (see Section 8.2.11).

Since the EU Directive is binding on all the Member States, there was a need for other countries to adopt this approach or a suitable alternative. In 1996, a similar code was adopted by the European Industrial Pharmacists Group. This code can be obtained from the Industrial Pharmacists Group at the Royal Pharmaceutical Society of Great Britain. However, in most of the Member States, disciplinary matters are dealt with by the regulatory authorities. This contrasts with the UK, where discipline is a joint responsibility of the regulatory authority and the appropriate professional body.

In the UK, it is generally assumed, although is not necessarily the case, that a QP is a member of an appropriate professional body and will thus be bound by the rules and guidelines of that body. Additionally, if a QP fails to carry out their duties in an appropriate manner, they can be considered to be guilty of professional misconduct and can have their professional status removed. Failure to adhere to the QP code of practice would be considered as such a case.

The code of practice emphasizes the fact that QPs have a responsibility not only to the companies that employ them, but also to the licensing authority and the inspectorate. They have a duty to highlight any aspects of the quality system that do not comply with requirements. Should an aspect of the situation in which they are being asked to operate be outside their sphere of knowledge and experience, they also have a duty to refuse to act in this context. For example, a QP whose only experience is in the manufacture of dry products would not automatically be competent to act as a QP if the company moved into the manufacture of sterile products.

8.2.4 Registration

There are two categories of person defined in the Directive who can be registered as eligible to serve as a QP. These are referred to as the permanent and transitional provisions. Under the permanent provisions, there is a definition of a specific course of study that must be undertaken (see Section 8.2.5) together with an appropriate period of work experience, before a person can be nominated for the role of QP.

However, at the time that the role of QP was being formalized across the EU, there were a large number of people who were already carrying out such a function within their companies. These people had experience in the role, but had not studied for the formal qualification. Under the transitional provisions, these people were permitted to apply for QP status on the basis of experience alone.

One issue currently being faced within Europe is that the QPs who were registered under the transitional provisions are coming to the end of their careers. This means that more people are leaving the register than are joining it. Owing to the major investment in time (by the candidate and their employer) and money (usually by the employer), there is a slow-down in people eligible for the role.

8.2.5 Training

The knowledge required by someone working towards eligibility via the permanent transitions (the only way now open to potential QPs in Europe) is very detailed and covers 12 major subject areas. Once again, there are differences in approach. Much of the knowledge required is covered by the pharmacy degree, although the amount of industrial pharmacy covered by these university courses is not always high.

There are a small number of institutes and training centres across Europe offering specific QP training, primarily in the UK. Training is generally modular and can be carried out in any order. Depending on the previous experience and qualifications of an individual, either the whole course or just some sections will be studied. This section reviews such an approach to training.

Pharmaceutical law and administration

This module covers the law within the home country and across the EU, together with relevant standards, guidelines and inspection initiatives such as PIC/S and ICH (see Chapter 11 for full details).

Medicinal chemistry and therapeutics

This module covers how the body functions, what happens when the functioning breaks down and the role of pharmaceuticals in the process.

Pharmaceutical formulation and processing

This module covers the different types of dosage forms and how they are formulated and manufactured. It also covers process validation. This is obviously a huge subject area, reflected in the fact that this module is twice as long as any of the others.

Pharmaceutical microbiology

This module provides a basic overview to microbiology and the methodology of disinfection and sterilization, as used within the pharmaceutical factory.

Active pharmaceutical ingredients

This module deals with the main processing stages in the manufacture of active pharmaceutical ingredients and the regulatory situation in such facilities.

Mathematics and statistics

This module covers the use of statistical techniques within the pharmaceutical industry.

Analysis and testing

This module deals with laboratory methodology and the validation of analytical techniques. It also covers good laboratory practice (see Chapter 1 for full details).

Pharmaceutical packaging

This module covers the design of pharmaceutical packs and the process of packaging.

Quality management systems
This modules reviews all the aspects of the quality system (as covered by Chapters 1–5 of this book) and some aspects of interpersonal skills.

Formulation, manufacturing and analysis
This is a practical module, during which there is an opportunity to practice manufacture and analysis of a number of types of pharmaceutical.

Investigational medicinal products
This module deals specifically with clinical trials, from the design of the trial itself, through the manufacture and release of the clinical trial materials.

The role and professional duties of a QP
This module covers the role of a QP from the legal, professional and ethical standpoints and reviews the code of practice.

8.2.6 Role of the qualified person

The role of the QP can be specifically described as ensuring the following.

- Each batch of product is manufactured in compliance with both the manufacturing authorization and the specific marketing authorization.
- Each batch of product imported from outside the EU has been fully tested to prove that it complies with all requirements of the marketing authorization.
- Each batch of product imported from a country outside the EU, where the EU has an agreement that products are manufactured to at least the same standard as that in the EU, can be accepted without carrying out additional testing.
- Each batch of product that is approved must be entered in an appropriate register as soon as possible after manufacture or importation.

8.2.7 Routine duties of the qualified person

In the process of approving a batch of product for release on to the marketplace, there are a number of checks that a QP must make to ensure that all the requirements have been achieved.

- The batch must comply with the requirements of the product licence and the manufacturing authorization.
- All aspects of GMP guidelines have been fulfilled.
- Critical processes have been validated.
- All quality control checks have been carried out satisfactorily, and a review of manufacturing and packaging records has been completed.
- Any process deviations have been recorded and investigated to determine the effect on product quality. (In some cases, depending on the nature of the deviation, this would imply notification to the national regulatory authority.)

- If required as a result of the process deviation mentioned above, all extra quality control checks have been carried out satisfactorily.
- The documentation review has been carried out and signed off by appropriately qualified personnel.
- Self-inspections and other regular audits have been carried out.
- All other aspects, such as calibration and environmental monitoring, are satisfactory.
- All legal aspects relating to products imported from outside the EU are covered as required.

Depending on the size of the company, the QP may carry out some or all of these checks personally. However, in larger organizations, it is acceptable, and indeed necessary, for the QP to rely on other people to carry out individual checks on a day-to-day basis. In this case, the principal responsibility of the QP is to ensure that the appropriate elements of the quality system are in place and that there are sufficient controls within the system to prevent problems being missed. Hence the QP relies on the activities of other people and has to have good interpersonal skills to maintain good relationships with these people.

The QP will also be involved in routine dealings with the regulatory authorities. In some of the Member States, this will be as part of a team. However, in France, the regulatory authority will only deal with the RP.

8.2.8 Requirements for number and location of qualified persons

According to the Directives and guidelines, companies are only required to nominate a single person to serve as a QP. However, in this case, there is no cover for holidays and/or sickness absences. Hence, unless there is only a very small number of batches for approval, in which case such an absence is not likely to be a problem, the company would need to identify a suitable alternative person as a deputy.

However, in the situation where an organization is a large one, or one that operates on more than one manufacturing site, it is permissible for a number of people to be nominated on the manufacturing authorization.

8.2.9 The qualified person and quality control

There is no specific requirement that the QP and the head of quality control be the same person. The EU guidelines specifically state that: ‘Key personnel include the Head of Production, the Head of Quality Control (QC) and . . .. the Qualified Person(s) (QP) designated for the purpose’ (EU GMP guide, paragraph 2.3).

Version 2 of the UK Code of Practice states: ‘It is acceptable and often helpful for the Quality Controller to be a Qualified Person’ (UK Code of Practice, paragraph 7.3).

In a small organization, it is quite likely that the same person would be responsible for QA, QC and be the QP. However, in a larger organization, QC is often one of the departments within the QA function. The QPs in this situation could be the head of QA and/or some of his or her deputies.

8.2.10 Contracted qualified persons

As mentioned previously, it is not a requirement that the QP is an employee of the company. It is acceptable for the QP to be working under contract to the company, in a self-employed status. This is particularly relevant for small companies, who may only have a few batches to be released each week and for whom the expense of employing a full-time QP would not be justified.

In such a situation, the responsibility of the QP in relation to the professional aspects of the role is exactly the same as if there were an employer–employee relationship. However, there should be a written contract between the two parties, detailing the expectations and responsibilities of both.

In addition to signing of batch releases, the QP would be expected to take part in training, auditing and other activities, and be in attendance during regulatory inspections.

8.2.11 Contract manufacture

In the situation where one company (the contract acceptor) is manufacturing a product under contract for a second company (the contract giver), there is no clear rule as to where the QP shall be located. It would normally be the case that the contract giver would hold the marketing authorization and the contract acceptor would hold the manufacturing authorization. The QP may be located in either company, but must have full access to all appropriate information from both parties. The arrangement must be clearly stated in the contract itself.

8.2.12 Continuing professional development

Many professional bodies nowadays require their members to carry out an element of CPD as a prerequisite to maintaining their membership. The three professional bodies involved in the drafting of the QP Code of Practice in UK are no exception to this rule. Their positions are spelt out in Annex 1 to the Code.

However, QPs, whether or they are members of a professional body, also have a responsibility to keep their knowledge and experience up to date. There is a requirement that a written record of this CPD is kept by the QP.

8.3 The equivalent role in the USA

There is no defined role of the qualified person in the USA. Responsibility for batch release sits with the quality control unit (21CFR211.22). By reviewing the various clauses of 21CFR211, it can be seen that all the requirements outlined as the routine duties of the QP are covered with the FDA rules. However, there is no link between the person signing the batch release certificate and a professional membership that can be withdrawn in the case of misconduct.

In the USA, the emphasis is on setting up the systems in the first place and validating those systems. Thereafter, the responsibility for batch release may be delegated to a technician in the quality control unit.

8.4 Other parts of the world

The PIC/S guide to GMP uses the term ‘authorized person’ in place of QP. In the glossary to this guide, the term is defined as: ‘Person recognized by the authority as having the necessary basic scientific and technical background and experience’.

Just as there are variations in the approach taken within different countries in Europe, so there are differences in other parts of the world. Some countries have no such official position in place. Many others will only accept pharmacists in the role. In all cases, the situation is a matter of national regulation.

9

Technology transfer

9.1 Introduction

Technology transfer is the process of commissioning and installing a new product or process in a manufacturing facility. It involves the transfer of documented knowledge and experience, built up during development and/or previous full-scale production, and requires a demonstration by the receiving facility of their ability to achieve all the critical parameters of the process. It is a major project activity that needs to be managed carefully if it is to be successful.

This chapter starts by reviewing some of the reasons why technology transfer is required. It then looks at the way in which companies chose where to relocate production. This is followed by consideration of both the hardware (i.e. equipment) aspects of technology transfer and the software aspects (processes and people). Issues such as validation and registration are discussed. A technology transfer guide, currently being developed by the International Society for Pharmaceutical Engineering (ISPE), is then introduced. Finally, there is a section on the need to maintain quality during a technology transfer programme triggered by a factory closure.

9.2 Reasons for technology transfer

Technology transfer occurs within the pharmaceutical industry for many different reasons, often very positive ones. When a multinational company develops a new product and the demand exceeds the capacity at the original manufacturing site, it often transfers the product to other factories within the group. When a product is nearing the end of its product life cycle, it may be moved from one of the strategic sites to other regional or local factories. When a company decides that outsourcing is a preferable alternative to refurbishment or expansion, it needs to transfer the technology to the contract manufacturer. On the other hand, when a factory is being closed, there will be a need to

transfer the production processes to other manufacturing sites before that closure takes place.

This section reviews each of these reasons in a little more detail.

9.2.1 Scale up and product launch

The early stages of product development are carried out at laboratory scale in the R & D department. This tends to be true, both for products being developed under patent, using a new chemical entity and for generic products that are being taken from the national pharmacopoeia.

In some companies, there is an intermediate stage, where pilot-scale production is carried out. Typically, this would be at one-tenth full production scale. To be truly effective, the equipment should be as close as possible to the type used in production.

The final stage of product development will always be carried out on the production equipment, since it is only at this point that the process parameters can be refined and confirmed. At this point in the life cycle of the product, the development personnel will be the ones who have most experience of the product characteristics, whilst the production personnel will generally be the experts in the use of the production equipment.

Technology transfer would typically take place during any experimental batches and the first couple of production batches produced on the plant. It is important that during this technology transfer, an effective handover of knowledge takes place, if ongoing production is going to be problem-free.

9.2.2 Extension of manufacturing base

This is based on where the products are going to be marketed. With the economic organizations, such as the EU, the North American Free Trade Agreement (NAFTA) or Mercosur in Latin America, significant tax and pricing advantages may be gained by manufacturing in one country for the whole of the region. On the other hand, there are trade barriers that can affect decisions. For a number of years, the Russian government has been threatening to impose a 30 per cent import tax on finished pharmaceuticals, which is tending to shape manufacturing strategy with respect to that country. There are also some countries, such as Mexico, where agreement of pricing may be affected significantly by whether products are manufactured in the home market or not.

Another issue to be considered is in relation to pack requirements. Where markets are relatively small and have specific pack requirements, such as language, it may be sensible to decouple bulk manufacture and packaging. For example, a single strategic site could be used to produce the global supply of a particular tablet, which could be shipped in bulk to individual markets for local packaging.

When relocating product manufacture from one country to another, it is important to consider the registration restrictions relating to third countries that currently provide a market for the product. In case study 1, a major market for one of the products was not prepared to purchase from the new manufacturing country. Any potential loss of market was factored into the decision to move the product to the new location.

9.2.3 Contracting out or licensing of product

These two options have been used by companies over the years, often as a first step into a new marketplace. They can be alternatives to building a new facility in countries where having local manufacture is a prerequisite for doing business.

Many companies are also using contracting out – termed more frequently as outsourcing – to supplement their own manufacturing capacity. This might be used in the case of a company that wishes to move older products, in order to free up capacity for the new drugs. Alternatively, it might be that a company has a product that requires specialized technology that is not part of their expertise.

In these situations, there needs to be close liaison between the technical team in the receiving factory and the staff from the company itself. The latter would either be from the development function, or from the manufacturing departments, depending on the age of the product and the resources available.

9.2.4 Sale of the product

When a product reaches the end of its product life cycle, in most industries it would be discontinued. However, in the pharmaceutical industry, this may not be possible, or indeed desirable. Markets mature at different rates and some countries have fewer resources to spend on new drugs than others do. Hence there will be cases where there is a small, ongoing need for a product. In this case, an option is to sell off the product to a local company. The process for technology transfer should be the same in this case as in contracting or licensing out.

9.2.5 Closure of factory

It is an inevitable fact of pharmaceutical manufacturing at this point in the industry's history that multiplant companies will decide to close one or more of their plants. This is becoming more of a trend with every merger that takes place. At the same time, some companies are deciding that manufacturing is no longer a core part of their business and are moving from in-house production to contract manufacturing.

Whatever the reason for the closure, it is preceded by a transfer of some or all of the products to an alternative manufacturing site. If this process is to be achieved in a satisfactory manner without severe consequences for quality in one or both of the plants, there are a number of key issues that need to be addressed.

A factory closure with ongoing manufacture at an alternative location is a project that can be divided into three main phases. Firstly, there is the pre-announcement planning phase; secondly, there is the phase of continuation of production in the closing facility from the time of announcement to the date of closure; and finally, there is the phase resulting in transfer of production from the closing facility to an alternative manufacturing site. Each of these phases has their own issues and management implications that must be dealt with if the project is to be successful.

9.3 Choosing the receiving site

The decisions to be taken as to where a company will transfer products to are often considered during the development of a manufacturing strategy.

As part of a strategic manufacturing study carried out in the mid-1990s by a multinational company, a benchmarking exercise was run with a number of major players to determine which were the main issues considered during strategy development. The responses showed that both technical and financial considerations were key. On the technical side, issues such as proximity to development resources, an ability to meet the required quality standards, and the opportunity for standardization and pack rationalization feature highly. On the financial side, aspects such as the ability to cut fixed costs, the minimization of capital expenditure, an ability to service key markets and the existence of tax advantages were important.

It is helpful if the organization has developed some common definitions of factory roles, such as strategic, regional server and local server. These definitions specify the level of autonomy in standard setting and relationships with R & D. They also set the tone for the type of product and packs to be made.

The study found that each company had different priorities for such considerations and the following list is by no means definitive. It does, however, cover some of the major areas.

9.3.1 Available capacity

In broad terms there needs to be sufficient capacity of the right type in the receiving site to cover the current workload and potential growth throughout the life of the plant. This is not to say that capital expenditure will not occur in the future, but any expenditure directly resulting from the transfer project must be factored in to the cost–benefit analysis. Consensus will have to be obtained on capacity measurement and particularly on the number of shifts that will be used. Experience has shown that this will have to be dictated by a central group. The number of shifts to be used should be two or three per day, and either five or seven days per week, according to local custom. The days of manufacturing plant only being utilized on a single shift basis are well and truly over.

9.3.2 Quality standards

In the 1970s and 1980s, there was a proliferation of construction projects and/or development of contract manufacturing relationships by the multinationals, resulting in the overcapacity that has led in part to the current trend for rationalization. Inevitably, facilities around the world are at different standards, even within the same companies (although this is not to suggest that a double standard exists in terms of the final product).

A technology transfer project is therefore an opportunity to ensure that optimal quality standards are maintained. Note the use of the word optimal, rather than maximum. There is a need to recognize that certain markets place additional requirements for quality on to the factories that supply them. However, to suggest the

imposition of FDA-level requirements in all factories around the world, serving all markets would be as inappropriate as aiming for lowest cost at the expense of quality.

9.3.3 Product costing

When comparing candidates for receiving product transfer, there is a temptation to compare product costing as an absolute measure of performance. This is only valid if the entire company has a rigidly applied, single costing system. This is rare, particularly in the pharmaceutical industry.

Thus the use of existing product costing data should be treated with caution. It may be worthwhile to recost the affected products against common criteria. The other simpler alternative could be to guarantee the markets served by the closing site that products will be made available at a cost no greater than the existing source of supply or even that they would be cheaper by x per cent.

9.3.4 Geographical/political considerations

This is based on where the products are going to be marketed. With economic organizations, such as the EU, NAFTA, or the recently signed Pan America treaty, significant tax and pricing advantages may be gained by manufacturing within the region without being in the same country.

On the other hand, there are trade barriers that can affect decisions. For several years in the mid-1990s, the Russian government was threatening to impose a 30 per cent import tax on finished pharmaceuticals. In the event, this was not carried through; however, there is a differential system of import tax, which is tending to shape manufacturing strategy with respect to that country. Currently, there are three levels of import duties on pharmaceuticals: 20 per cent for finished pharmaceuticals that can already be sourced in Russia to an acceptable quality; 10 per cent for all other finished pharmaceuticals; and 5 per cent for semi-finished pharmaceuticals and raw active ingredients.

There are also some countries, such as Mexico, where agreement of pricing may be affected significantly by whether products are manufactured in the home market or not.

Another issue to be considered is in relation to pack requirements. Where markets are relatively small and have specific pack requirements, such as language, it may be sensible to decouple bulk manufacture and packaging. For example, a single strategic site could be used to produce the global supply of a particular tablet, which could be shipped in bulk to individual markets for local packaging.

When relocating product manufacture from one country to another, it is important to consider the registration restrictions relating to third countries that currently provide a market for the product. If a major market for one of the products were not prepared to purchase from the new manufacturing country, this would have a significant effect on the decision. Any potential loss of market must be factored into the decision to move the product to the new location.

9.3.5 Market perceptions

Company rationalization programmes are often carried out on a regional basis. When considering using a particular country to supply other countries within a region, it is important to consider the perception of that country throughout the rest of the region. For example, in the early 1990s, any Latin American strategy that centred on using Mexico to supply other parts of the region was faced with the issue that poor-quality packaging materials had traditionally led to Mexico having a reputation for poor-quality product within Latin America. Today, in many parts of the former Soviet Union, product produced locally will be seen as inferior to imports, even in cases where the perception is incorrect.

9.4 Evaluating the hardware and software issues

In some technology transfer projects, it is a case of moving the products only from their existing manufacturing site to an alternative one. In this case, it is better where the equipment in the receiving site is the same, or very similar to that in the originating site. If this is not the case, a degree of reformulation is likely to be necessary.

However, there are some projects where the existing production line is to be relocated in the new site or where a new line is to be installed. This adds a whole new dimension to the situation.

9.4.1 Identifying costs

It is quite likely that the transfer into a plant of a new line or lines will require some refitting. It is essential that this is recognized at the cost–benefit analysis stage and included in the calculations.

In the case of a project involving a factory closure, it is likely that initial discussions will take place over a period of time prior to the announcement and that these discussions will involve very few people. As a result, the planning phase can suffer from a lack of accurate data and costing in particular. In this case, the perceived need for secrecy can result in a loss of quality information.

9.4.2 Attention to detail

Consideration of product transfer requires a close attention to detail. In comparing product listings between factories, it may appear at first sight that the same products are being made. However, it has been found that examination of each product in detail is necessary as early as possible. Even if the formulation is the same, has there been any drift since launch? Is the tablet design identical? Are the packaging details the same? Once differences are detected – and there will be differences – the implications for registration and refitting can be determined.

9.4.3 Asking for help

It has to be recognized by the new site of manufacture, that in the case of an old, established product, there is a high level of knowledge within the previous production team, and it is not a sign of weakness to ask for and utilize this knowledge. In two different cases observed in the past, this was handled differently with interesting results. In one project, full discussions took place with the 'experts' from the handover site and the plant design benefited from this. Handover was smooth and everyone felt that his or her experience had been recognized. In the second project, there was virtually no discussion and the plant was redesigned without taking into account the lessons learnt over a 20-year period. Whether through ignorance or arrogance, the original staff were completely alienated by the process, and handover was much more protracted and problematical.

9.4.4 Soft systems

It should also be remembered that refitting might involve not only the physical plant, but the soft systems as well. Can the logistical software handle the products, or are changes needed to the software? Do the new markets require specific packing or shipping details or documents? Are there limitations on payment from the new market that can affect the operating systems of the new location? Finally, what impact will there be on training requirements – and indeed, staffing levels? A smooth transfer of production will be hampered at the last minute if the contractor's software cannot handle the new product range. This could result in stock-outs in the marketplace, despite product being approved and available for dispatch from the warehouse.

9.5 Validation and registration

9.5.1 Validation

In terms of validating the product transfer, the level of work required will depend on a number of things. Does the transfer involve a range of new products or simply an increase in volume of an identical range? Is it an additional set of products for an existing range? Is it alternatively a completely new type of production? Finally, what level of validation has already been carried out in the original site of manufacture?

There is also a temptation to use the opportunity of product transfer to improve on the process in some way. However, this should be balanced against the validation implications of making too many changes at one time. If speed of transfer is critical, then the number of changes that are made should be kept to an absolute minimum. In some closure projects, entire manufacturing suites may be transferred from the closing site to the factory that is taking on the products. By restricting any process changes, the validation requirements are limited and hence do not take up too much time.

Frequently there may be regulatory reasons why the existing product has to be manufactured in the same way as previously. Staff at the new location need to understand these reasons, and continue to adhere to them even if there is a corresponding increase in costs or complexity.

9.5.2 Registration

There are two main areas of consideration in terms of registration, particularly if the transfer of production is across national boundaries: the needs of the new manufacturer, and the needs of the final marketplace.

In terms of the new manufacturer, registration requirements should have been considered at the time of the assessment. For example, the use of a factory in the USA to supply other parts of the world will have implications for cost and timescales as all products have to be registered for sale in the USA as well as in all final markets, even if the product is only to be exported. On the other hand, products manufactured in EU countries only have to be registered for the countries in which they are to be sold.

In terms of the marketplace, there may be a need to understand local requirements, even if these seem unreasonable to the receiving site. It can become very frustrating for the people in each of these markets when the facilities that are going to take over manufacturing fail to accept the need for things that they do not supply to other countries. For example, the Medicines Control Council (MCC) in South Africa is very strict about notification of process changes, even down to requiring information of one-off process deviations. This is not common in other countries and hence some sites would find it difficult to comply with such a request.

It has to be accepted by the new site of manufacture that these extra requirements are a necessary result of the closure decision. Identification of such requirements early in the process is essential as registration is frequently on the critical path of the project plan.

9.6 The technology transfer guide

There is a huge amount of technology transfer being carried out within the pharmaceutical industry at present and very little guidance on how to do it effectively. Therefore, the ISPE in collaboration with the FDA and the American Association of Pharmaceutical Scientists (AAPS), and with input from the European regulatory authorities and submission to the Japanese Ministry of Health and Welfare (MHW), have created a user-friendly document that presents a clear and concise general process for transferring technology between two parties. The guide has been designed to present a standardized process and recommends a minimum base of documentation in support of the transfer request. The guide is divided into three segments: active pharmaceutical ingredients, dosage forms, and analytical methods.

9.7 Planning for a successful technology transfer

The process of technology transfer between two sites may be defined as a project and, like any other project, the key to success lies in the planning stage. There needs to be an overall project plan, covering all aspects of the transfer. In particular, there should be a detailed training plan to ensure that by the end of the transfer, the receiving site will be able to demonstrate competence in manufacturing the product in question.

Of particular importance is the product information dossier that will contain the accumulation of data regarding the product from development onwards. This dossier will include information on at least the following items:

- product characteristics;
- packaging specifications;
- formulation rationale;
- stability data;
- raw materials, both actives and excipients;
- process details and critical process parameters;
- product performance report (if the product has already been manufactured elsewhere);
- facility and equipment requirements;
- qualification and validation reports;
- analytical test methodology;
- environmental and safety assessments.

9.8 Maintaining quality during factory closure

This section draws on observations made and lessons learnt during a number of factory closures. In particular, it deals with the closure of three factories in different parts of the world. It can be seen that there are obvious cultural differences between the cases and these should be taken into consideration in drawing conclusions. However, there do appear to be a number of generic messages coming out of each project that can be applied to future rationalization activities.

Case study 1

Case study 1 relates to a closure of an entire factory in mainland Europe, with transfer of production to factories around Europe, including the UK. The sales and marketing operation, plus quality assurance functions were retained at the original site.

Case study 2

Case study 2 relates to the closure of a plant in the UK, with transfer of production to other European sites, mainly in the UK, but also in mainland Europe. All functions on the original site were shut down and the site was disposed of.

Case study 3

Case study 3 relates to closure of a factory in South Africa, with production being split between a local contract manufacturer and other plants belonging to the parent company all around the world.

9.8.1 Retaining the support of the existing workforce

Openness versus secrecy

A potential factory closure is obviously a highly sensitive subject. At the point where an assessment of the situation is still being made, the desire to keep the discussions as secret

as possible is understandable. However, this secrecy will have implications that must be recognized.

In case study 1, the discussions took place between senior managers from head office and the local team, together with internal consultants. At some point, external consultants were also involved, but not all the team was aware of this. Hence, the secrecy extended even to the assessment team in part. This had to be properly managed to meet the requirements of the national social legislation.

In case study 3, only a small number of senior managers were involved in the pre-announcement discussions. This was a high-risk strategy for the company, as, by South African law, any decision on retrenchment should be preceded by a chance for the workforce to offer an alternative solution. In order to get around this problem, the management came to an agreement with the workforce that had implications for subsequent stages of the process, as will be discussed later.

The decision on when to 'go public' is one of balance, timing, local legislation and trade union relations. Who are the right people to involve and when? However, there are examples when everyone was aware of what was being discussed (e.g. during activity value analysis processes so much in vogue in the early 1990s) and this was not necessarily a major problem. In fact, in the post-merger situations experienced within major multinationals, such as GlaxoWellcome and SmithKline Beecham, everyone knew that everything was being assessed, so in theory there should be no major surprises. (This is not to trivialize the huge personal trauma that can be experienced by an individual who finds that their services are no longer required by an organization. It merely questions the validity of keeping the discussions secret for a long period prior to announcements being made.) Since the two companies referred to above have recently merged to form GlaxoSmithKline, it will be interesting to observe what lessons, if any, they learnt from the previous exercises and whether they do things any differently this time around.

Expectations versus reality

Not withstanding the wish to keep discussions secret, rumours spread very quickly, particularly if there is an unusually high incidence of visits from group personnel or external consultants. It is often the case that not knowing is worse than knowing. When the announcement was made in case study 3, the general reaction was 'at least I now know what is going to happen and can start planning the rest of my life accordingly'.

It must also be recognized that, once the announcement has been made, there is no going back. In case study 3, the decision to close the plant was a side effect of an ongoing programme of collaborations between two companies. In the event, the negotiations on collaboration within Southern Africa broke down some weeks after the closure announcement had been made. Hence the original cause of the closure had gone away. However, by that time it was too late to reverse the closure: it had already started to become a reality.

It should be remembered that not only the people in the factory itself are affected by the closure. In both case studies 1 and 3, there were examples of senior managers who were on secondment overseas at the time of the announcement. At a stroke, their obvious return routes home were eliminated. In a case like this, it is the responsibility of the human resources (HR) function at head office to ensure that such individuals are looked after, particularly if the local HR function is a casualty of the closure. The trauma of losing one's

position is greatly intensified if one is working in a foreign country without obvious support mechanisms.

In general, it is better for very short, demanding timescales to be set for implementation. The reason for this is to engage the existing staff fully in the project but for the shortest time possible in order to allow them to plan for their own futures.

Incentives

In order to keep the plant running to the end, there will be a need to keep at least some, if not all, of the workforce employed until the closure date. In a situation where everyone is inevitably putting their own interests before those of the company, this may be difficult to achieve. In case study 1, an agreement was reached, in that a generous severance package was available, but only if the staff stayed until the end. There were virtually no losses as a result prior to the closure date.

In case study 3, as a result of the secrecy issue discussed earlier, an agreement was made that all contracts would be terminated and severance packages made available from six months prior to closure. Staff members were then re-employed on six-month temporary contracts. Consequently, there was no incentive for people to stay with the company once they had found alternative employment. The loss of staff, particularly in the middle management levels, was considerable, just at the time when extra resources were needed to keep things going smoothly.

The receiving plant personnel also need to have some incentives. This may sound surprising but they do need to understand that their future is also not guaranteed as a right. They have to be able to deliver what the new customer wants.

Technical support

It was necessary with both case studies 1 and 3 to provide technical support from other parts of the main companies. In case study 1, a senior technical manager left six months prior to closure. An experienced production manager from the head office internal consultancy group was seconded to the post for six months. This had the advantages of putting in post someone who was committed to making the project successful, had no fear for his own future to affect his performance adversely and also created a bridge with the main site in UK to which much of the production was being transferred. The individual also had an awareness of the issues involved in the closing factory and was able to understand what was needed to support it.

In case study 3, the senior managers remained in post, but many of the junior and supervisory staff left at the early stages. This resulted in a requirement for considerable input of technical support to keep the factory going on a day-to-day basis. A permanent presence in the laboratory was provided by the company's central QA function and at various times, supervisory support was provided from the UK, Pakistan and Australia. For many of these individuals it was an ideal career development opportunity. With a multinational company it should be remembered that not all the talent and experience resides in the country where the head office is located.

One further opportunity is provided by the need for support in the closing unit: it can be used to help the production transfer process. In case study 3, one of the people who spent time working in the plant came from the manufacturing area in Australia that was due to take on manufacture of many of the products. Whilst providing support, he was also

learning about the products for the future. Again, the importance of a bridge with the receiving plant is critical.

Improvement versus maintenance

The following points are to a certain extent culture dependent. However, it is likely that, to a degree, they will apply in any factory being closed down. Once the announcement had been made in case study 3, all improvement activities stopped dead. In fact, it was difficult to obtain maintenance of basic systems such as procedure writing. The role of QA became particularly vital at this point. They gave the lead in keeping systems operating with particular emphasis on self-inspection by production/QA teams. In the final months, these self-inspections were moved from a monthly to a weekly cycle.

Management versus policing

It is also possible that the style of management may need to change to more of a policing role. In factory closure projects, a number of security incidents sometimes occur that can be directly related either to people taking less responsibility for their actions or deliberately causing problems as a way of expressing their frustration. It may be necessary to increase the level of supervision to prevent this sort of incident occurring.

On the other hand, in other closure projects that have been observed, the workforce maintain their pride in the job and hence their responsibility for their actions until the end. This was particularly evident with some teams in case study 2. In many respects this is due to the way in which the total project is managed.

Continuity

In each of the closures being discussed, it has been found that anyone who has a guaranteed role in the future organization is key to the success of the transfer phase of the project.

The situation with the registration manager in case study 3 has already been referred to. In case study 1, the QA manager was to stay on as the only technical representative after the factory closed. In case study 2, one of the senior technical managers was transferred to one of the receiving sites to run the areas that had taken on the work. All these people played a significant role in seeing the projects through.

Cannibalization

If a factory is closing down, it is inevitable that decisions will have to be taken about disposal of equipment, whether to the new site of manufacture or elsewhere in the group. An element of sensitivity should be exercised in dealing with this. People walking around the production areas with tape measures, as happened in case study 1, can cause a high degree of resentment if not handled properly.

9.8.2 Stock building versus rapid closure

Given the difficulties experienced in keeping a factory running once the closure announcement has been made, there is a case for implementing the closure as quickly as

possible. In case study 1, the general manager wanted to implement the closure over a period of three months. This was not found to be possible; however, everything was completed in nine months. In case study 2, the whole project took two years and, towards the end of that period, there were only a few people left, keeping the last few processes running. For these people, the atmosphere was poor and the working environment left much to be desired.

The decision to close a factory is obviously a tough one. However, once it has been taken, it is advisable to implement it as humanely as possible, not only for the obvious humanitarian reasons, but also because a closure takes a finite period of time (from experience, at least six to nine months) and production needs to be maintained during that time.

It is possible to make allowances for a delay in start-up by increasing the level of stock build prior to closing. In fact, if the transfer of production is to be accompanied by a transfer of critical plant or machinery, a stock build is essential. In case study 1, despite a stock build exercise, some stock-outs did occur. All delivery promises from new manufacturing sites must be kept, otherwise logistics will fall apart. The new site must understand the consequences for them of failure to maintain agreed schedules. Changes in requirements must be negotiated with the marketing organization and the receiving location.

It should also be remembered that building stock over and above normal production levels is difficult at the best of times, assuming that the plant is operating at anywhere near full capacity. It requires hard work and goodwill amongst the workforce and frequently results in significant amounts of overtime being worked. To achieve this in the context of closure could be even more difficult.

Finally, it should be made clear to the sales and marketing departments why the stock build is taking place. The manufacturing staff of a factory in Latin America made the mistake of not explaining the situation some years ago. They had worked very hard to build up stock in advance of a major project to refurbish parts of the factory. (A much more positive reason to build stock than as a precursor to closure.) However, the sales representative observed the stock levels rising in the warehouse and went out to their customers with special sales drives. As a result, sales rose considerably and the refurbishment was delayed whilst production did it all again!

9.8.3 Management of the implementation

Management commitment

The decision to close a factory is taken at the highest level in the company, although hopefully with the full knowledge and agreement of the senior management within the unit. Once that decision has been taken, however, it must be implemented by the local management. In case study 1, the general manager was far from happy with the decision, but once it had been taken, he was fully committed to carrying it through successfully, without damaging the business in the country. His involvement in and sponsorship of the latter stages of the project were invaluable. In fact, it can be concluded that, if the senior management team is not committed to making the closure happen effectively, they should be replaced by a team that is. Anything less will frustrate the ability of the company to meet its objectives for the closure.

Priorities

To the unit that is closing, activities associated with transfer of production constitute the number one priority, albeit in parallel with keeping the market satisfied in the interim. However, for the new site of manufacture, this is not likely to be the case. It is often a much larger site, with many products, both new and old. The activities such as registration and pack design may come some way down the priority list. Reconciling these differences of approach is very much a people issue – and one that should be addressed at an early stage, so that sufficient resources can be allocated. It has been found that a neutral, knowledgeable individual who can work in both units is most helpful (some would say essential) in ensuring that the receiving unit understands the priorities of the closing unit and responds appropriately.

Deadlines

Following on from the previous point about priorities, the transfer will be working to a series of deadlines. There is a tendency for these to be set by the unit that is closing, based on their view of the appropriate closing date. However, this can then require amendment as other aspects are taken account of. For example, in case study 3, the closure date was calculated on the basis of registration lead-times and then agreed with the workforce as part of the severance negotiations. Once delays were apparent with certain aspects of registration, the date for start-up of production was seen to be slipping back. A decision had thus to be taken on whether the closure date should also be amended. It is, however, vital that delay is not just accepted as something about which nothing can be done. Otherwise the project will never be completed. Good relationships with government can assist in the process.

Divided attention

Transferring production from one pharmaceutical factory to another is a major project and is probably a full-time job, at least for part of the time period. Running a factory is also a full-time job. Trying to combine these two roles could be a recipe for disaster.

In case study 2, the transfer project was split into a number of subprojects, each led by a different person. In case study 3, a slightly different approach was taken. A consultant was employed from the start to handle the legal and other commercial aspects of the project. The technical director maintained control of much of the rest of the transfer. However, recognizing that this could lead to him taking his eye off the ball in the old factory, he appointed one of his senior managers to stand in for him on a day-to-day basis. In case study 1, an internal consultant from head office was drafted in to provide the resource necessary.

New products versus old

It must be remembered that during all phases of a closure project, business must carry on as usual. This means that not only will the old products need to be supplied, but launch of new products will also be occurring. The resource implications of this should be recognized and allowed for.

Low demand products

In any manufacturing site, the product listing will include a number of ‘old favourites’, which for various reasons are still produced, even though the commercial case is weak. A

closure project is an opportunity to revisit this issue, and the discussion should be held early in the process with finance and marketing to avoid unnecessary waste of time and resources later on.

In case study 2, a particular product was identified for which special equipment was required. The sales were quite low, but marketing insisted that the product should remain on the range. A new site was identified but, owing to the weight of the equipment, some structural alterations to the building were required. Transport was costed and planned, as was the construction. At the last minute, marketing changed their minds and the product was dropped from the range. If the original decision had been challenged more vigorously at the start, much time and money could have been saved.

Project management

Throughout this section, closures have been referred to as projects and it should be emphasized that, like any project, its management is critical. In the closing site, a project manager is required, as has been discussed previously and the use of project management software may be found to be advantageous. In addition, the receiving site will require someone responsible for making things happen. With each of the closures described here, there was a significant amount of work for a number of departments in the receiving sites (e.g. registration and pack development). In case studies 1 and 3 in particular, it was necessary for a project manager to act as a link between the closing unit and the receiving site.

Project sponsorship

Finally, each project requires a sponsor who in the final analysis can bring pressure to bear if the project is not going to plan. This will often be a member of the executive who authorized the closure in the first place. In case study 1, the local general manager and the main board director for the region jointly took this role. Since the latter was also responsible for all the receiving sites, he was able to resolve issues of conflict very quickly.

In case study 3, the local general manager and the regional manager at head office jointly took the role. However, as neither of these had responsibility for any of the receiving sites, there was less strength in their position and issues still took time and influencing skills to resolve on occasion.

The overall message of this section is that closing down a factory is not easy, quick or cheap. It needs careful planning and appropriate allocation of resources if it is to be achieved successfully. Above all else, personnel are required who can operate under pressure in difficult situations and yet maintain relationships at the very time when they are under the greatest threat.

10

Calibration

10.1 Introduction

Within the pharmaceutical industry, measurement is a major activity. Measurements are taken of: time; linear dimensions; mass or weight; temperature; volume or capacity; velocity or speed; pressure; heat; electrical values, such as current, voltage and resistance; and many other things.

Consequently, there is a high level of instrumentation used in the pharmaceutical industry. An instrument is defined as the device used to measure a parameter. It will typically display the value or condition of the parameter and/or feed a signal representing the value or condition to an alarm, controlling device or system.

This instrumentation has a number of uses:

- Monitoring and recording process parameters e.g. a pressure gauge on an autoclave.
- Monitoring and recording environmental conditions, e.g. a particle counter.
- Controlling process equipment, e.g. a temperature control on a manufacturing reactor.

In all cases, the accuracy of the instruments is a critical factor in ensuring that manufacturing continues to take place in a controlled manner and hence the validated status of all processes is maintained.

The process of ensuring that instrumentation maintains its accuracy is known as calibration. In this chapter, there is a review of the type of calibration programme that a typical plant would have in place. This is followed by discussions of documentation, classification of instruments and the calibration laboratory. The chapter closes with a section on the training of calibration technicians.

10.2 Objectives of calibration

The definition of calibration is as follows: ‘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' (*EU Guide to GMP*).

The objectives of calibration are two-fold:

- To review the degree of error between a reading taken from an operational instrument and the same reading taken from a standard instrument.
- To alter the operational instrument in order to reduce the degree of error to zero or an acceptable level.

Calibration should be considered as one part of the ongoing validation of a facility. It will cover both the production departments and the laboratories.

10.3 Calibration programme

All companies should have a formal programme for the calibration of its instruments. In summary, the programme has a number of stages, all of which need to be addressed:

- All the pieces of equipment that can be defined as instruments are identified.
- A full list of these instruments is produced.
- For each one, the appropriate category is identified (critical, major or reference).
- For each one, tolerance and acceptance limits are determined.
- Written procedures are developed and authorized. These will vary depending on the category of instrumentation.
- The programme is defined in terms of schedule and frequency.
- Responsibilities are assigned for the various calibrations.
- Contracts are set up for any calibrations that need to be outsourced.
- Resources, including manpower and equipment, are provided.
- Calibration is carried out and records kept.
- Calibration equipment is maintained in an appropriate manner.

There will be a number of elements to this programme, each of which is considered below.

10.3.1 Calibration documentation

All companies prepare their documentation in a manner specific to their own policies and procedures. However, there will be a number of generic documents required for the calibration programme. These will include a master list or inventory of all instrumentation within the company; specifications relating to the performance of each instrument; standard operating procedures for the calibration of each type of instrument; a planning programme listing the individual calibrations to be carried out (preferably as part of the formal planned preventative maintenance programme of the company); the records of calibrations that have been carried out internally within the company; calibration certificates issued internally or by external bodies carrying out calibration on behalf of the company; and training plans and records for the calibration technicians.

All calibration records and certificates constitute GMP records and hence should be completed, stored and archived in accordance with documentation procedures.

Instrument calibration index

The purpose of this document is to catalogue all instruments on a calibration regime and to trigger the execution of the calibrations at the predetermined times. It should contain a record for each instrument requiring periodic calibration. Each record should include: the last due date, the last calibration date, the expiry date, the (next) due date, and the calibration period. Wherever possible, due dates should be planned to coincide with manufacturing plant planned shutdown dates or preventive maintenance dates.

Specifications

The specification for calibration of an individual instrument is very important and requires appropriate authorization and control. In particular, there are a number of key factors:

- The category of the instrument (see below for full definitions of each category): a critical instrument will be treated significantly differently from a major or a reference instrument.
- Accuracy and range: these should be set to meet the minimum needs of the parameter being measured.
- Calibration period: this should be arrived at to give a reasonable balance between over-frequent calibration and 'as-found' failures. It may include consideration of, for example: the durability and stability of the instrument; the required accuracy; the nature of the environment and usage; and the degree of criticality of the measured parameter.

Calibration instruction sheet

The calibration instruction sheet is the standard operating procedure, which states how to calibrate an instrument. It should contain all the instructions necessary to ensure that a competent craftsperson following the instructions will correctly calibrate the instrument. Each calibration instruction sheet should have a unique identity and the appropriate one for each instrument should be included on the instrument calibration index.

The calibration instruction sheet should be signed by the appropriate functions within the company to indicate acceptance of the calibration instructions, the category rating, the accuracy and range. These would include the instrument specialist, a product or process specialist and a representative of quality assurance.

Any changes to the format of the calibration instruction sheet should be authorized by the same signatories. The revisions should be recorded on a revision-tracking sheet, which should list all the material changes from the previous version and a rationale for each.

Worksheet log

This is a record of every worksheet produced and should indicate the date it was created, the due date and, when completed, the date of completion.

Proforma worksheet

This is a blank checklist containing instructions common to a particular type of instrument calibration and is used to produce individual, numbered worksheets. It will contain sections for the technician performing the calibration to enter the following as necessary: responses to questions; test instrument numbers; deviation numbers; any other document references; results of tests; and spaces for indicating completion of tasks with initials and date.

There should be sufficient of these to cover all types of calibrations, such as: '*in-situ*' calibration, bench calibration and despatch to an external calibrating house.

Worksheets

The worksheet performs two separate functions. Firstly, it is the instruction to carry out a calibration on a specified instrument in a specified time, i.e. it is analogous to a works order. Secondly, after execution of the calibration, it is the record of the work carried out, including the tasks performed, the person doing the work, and any unusual actions taken, i.e. once completed it will become part of the service history of the instrument.

Worksheets should be generated when the instrument calibration index is reviewed. They are generated from the proforma worksheet appropriate to the type of calibration. Each worksheet needs to have a unique number taken from the worksheet log (in effect a works order number). It should be clearly marked on each page of the worksheet. The worksheet should also make reference to the tag number of the instrument, the calibration due date and the appropriate calibration instruction sheet.

Generating worksheets

The instrument calibration index should be reviewed at intervals no greater than monthly to determine all instruments with a due date before the end of the following month.

For each calibration identified, a worksheet should be produced, which is given a unique number and recorded in the worksheet log. At the same time, the instrument calibration index should be updated to flag the existence of the worksheet.

Calibration certificates

Calibrations certificates should only be issued (or adopted if externally generated) for calibrations that meet the accuracy requirements laid down in the appropriate specification.

Calibration certificates should have a unique certificate number, and give a clear indication of the tag number and plant number or manufacturer's serial number of the instrument.

Certificates should be traceable to a national standard, by detailing the identity of the test equipment used; or derived from acceptable values of natural physical constants, such as those provided for in British Standard BS EN 30012–1. They should contain the date that calibration was carried out, together with the next due date and date of expiry of the calibration. There should also be an indication of the person who carried out the calibration and that person's signature to indicate responsibility for the accuracy of the information on the certificate.

Externally produced calibration certificates may not have all the above information. To be adopted they must have the missing information added by hand to complete the minimum requirements. This should be added by a member of the company's internal instrument group and signed and dated.

10.3.2 Instrument tagging

An instrument tag is the unique identifier that applies to each instrument location within the manufacturing plant. Each instrument should be labelled with such a tag carrying a

summary of the calibration history of that instrument. The tag should carry such information as the identification number of the instrument; the date of the previous calibration; the due date for the next calibration; and the signature of the calibration technician.

10.3.3 Carrying out calibration

The calibration should be carried out following the instructions in the appropriate calibration instruction sheet and the required responses on the worksheet completed.

First of all, the 'as-found' condition is determined. This is defined as the accuracy of the instrument over the required range before any calibrating adjustment or repairs are made. If this is outside the limits specified on the calibration certificate, it may indicate that faulty product has been produced since the instrument was last known to have been correct. To address this possibility, a deviation should be raised in accordance with procedure. It may also be necessary to place on hold any product batches that may consequentially have suspect quality, depending on the nature of the instrument in question.

The instrument is then calibrated and a final 'as-left' condition determined. This is defined as the accuracy of the instrument over the required range after calibration. If the 'as-left' condition meets the accuracy requirements, the calibration certificate is completed, and a calibration sticker indicating the calibration date affixed in a prominent position.

If the 'as-left' condition does not meet the accuracy requirements, the technician raises a deviation. The deviation shall address the controls to be used to ensure that the instrument is not used for drug products and the actions to repair or replace it. The technician shall therefore, in conjunction with departmental personnel, establish if it is necessary to put the associated manufacturing plant on 'hold' to prevent inadvertent usage on drug products.

When the calibration is carried out and the worksheet is completed, the worksheet log is updated to show the completion date and the instrument calibration index is updated to the new calibration date.

All instruments covered by the calibration programme should be calibrated prior to the expiry date. If a critical instrument were used on drug products when its calibration has expired, a deviation would need to be raised, which would address the risk to product quality of the batches made during the time that the calibration of the instrument has expired. If such an instrument cannot be immediately calibrated or replaced by one that is calibrated, the piece of manufacturing plant to which it relates should be put on 'hold' to prevent inadvertent usage on drug products unless an approved deviation allows continued use.

Recalibration may be carried out as part of preventive maintenance procedures, in which case a calibration instruction sheet and worksheet would not be needed. However, a calibration certificate should still be generated.

External parties (individuals or organizations) may be used for calibrating or repairing instruments. Where they are used, they should be monitored by internal personnel in order to ensure that the company's procedure for the control of external parties is being met.

10.3.4 Review of data

When a calibration is carried out, the data obtained should be reviewed. There should be communication at this point between the calibration department and the relevant department, whether in production or the laboratories. If the calibration is carried out successfully, it may only be necessary to confirm that the calibration programme is up to date. However, if there is a problem with any of the instruments, more detailed information should be provided.

10.4 Different types of standards

There is a hierarchy of standards used within calibration.

10.4.1 Absolute standards and international standards

These are the ultimate standards against which all reference equipment is calibrated.

10.4.2 Primary standard

This is the main reference equipment used to calibrate the rest of the instrumentation. It is either maintained at the appropriate national testing laboratory or kept at the company, and is used as the reference standard against which the company secondary standards are calibrated. It is generally four times more accurate than the secondary standard.

10.4.3 Secondary standard

This is the calibration standard maintained within the company, which is used to carry out routine calibrations. It is generally four times more accurate than the measuring standard.

10.4.4 Measuring standard

This is the instrument used for routine measurement and control within the company.

10.5 Different types of calibration equipment

The types of equipment found in a calibration laboratory will vary with the type of operations that the company is carrying out and the types of instrumentation that is installed around the premises. However, the sort of equipment required will include those shown in Table 10.1, which is adapted from the one presented in the Organization of Pharmaceutical Producers of India (OPPI) quality assurance guide.

Table 10.1 Calibration equipment

Calibration Equipment	Relevant Instrumentation
Universal calibrator	Digital equipment
Stable thermobath	Temperature gauges
Dead weight tester Pressure gauge Vacuum gauge	Pressure and vacuum gauges
Multipoint temperature scanner and printer	Autoclaves, ovens and sterilizing tunnels
Conductivity calibration jig	Conductivity meter
Standard solution kit	pH meter

10.6 Maintenance of calibration equipment

It is important that calibration equipment is stored and handled in an appropriate manner. As a minimum, the temperature and the humidity of the calibration laboratory should be controlled. The influence of other environmental conditions such as vibrations should also be considered.

10.7 Categorization of instrumentation

The frequency of calibration of individual instruments will vary depending on circumstances, such as: the pattern of usage; the sensitivity of the process being controlled and/or monitored; the recommendations within the manufacturer's operation and maintenance manual; and the history of previous calibration performance. For example, an instrument that has been shown to maintain its previous calibration state over a period of more than six months would not necessarily need to be calibrated on a quarterly basis.

However, the key point to be considered in determining frequency of calibration is the process that is being controlled and/or monitored and, in particular, the importance of the level of accuracy obtained. There are three categories of instrumentation as follows.

10.7.1 Critical instruments

These are instruments whose performance will affect both the process and the product. An example of such an instrument would be a temperature control on an autoclave. These instruments would generally be calibrated at least six monthly.

10.7.2 Major instruments

These are instruments whose performance will affect either the process or the product. An example of such an instrument would be a balance in the dispensary. These instruments

(and, in the context of calibration, a balance may be considered as an instrument) would generally be calibrated at least annually.

10.7.3 Reference instruments

These are instruments that are installed as reference points only and whose performance does not affect either the process or the product. An example of such an instrument would be a thermometer in an ambient condition warehouse where temperature is monitored but not controlled. These instruments would generally be calibrated on installation but not afterwards.

10.8 Purchase of new instruments

When a new instrument is purchased, there are a number of steps that should be taken. Firstly, the instrument should be identified and the instrument group informed so that they can issue a tag number. Secondly, it must be categorized as either critical, major or reference. This categorization and the rationale behind it is recorded and authorized, ensuring that the decision is consistent with company policy.

All critical instruments should be purchased with current calibration certificates that cover appropriate accuracy and range, and state a specific expiry date. These certificates must be traceable to national standards. If certificates cannot be supplied with the instrument, there will be a need to carry out initial calibration.

10.9 Review of calibration programme

On an annual basis, it is a good idea to review the calibration programme to ensure that it is still appropriate and effective. There are two key elements that should be reviewed. Firstly, the frequency of calibration of individual instruments needs to be determined. As mentioned above, the history of previous calibrations should be taken into account when determining the most appropriate frequency of calibration. There may be some instruments for which a recategorization is appropriate.

Secondly, this would be the time to review standard operating procedures to determine whether they need to be amended. For example, the procedure is generally written such that the instrument is tested across the whole of its operational range. However, if an instrument is normally used to measure around one focal point in the range, it may be more appropriate to concentrate the taking of readings around this point.

10.10 Training of calibration technicians

It is necessary to have in place a training programme that covers not only the people carrying out the calibration, but also the people reviewing the data to ensure that there is full understanding. Like any other part of the training programme, there should be a written training plan and full records of all the training that has already been completed.

In this way, the company is able to monitor the skills pool available and the ongoing plans to maintain that pool.

Training should be carried out when a person commences a role and also on a regular basis thereafter. Refresher training on at least an annual basis is recommended in order to check that standard operating procedures are carried out in the correct manner and that no bad habits have been learned over time.

When a new piece of instrumentation is purchased and installed, it is important to ensure that all relevant personnel are trained in the new methodology relating to calibration.

10.11 References to calibration in international standards

The references to calibration in the international GMP standards are relatively minor. In the EU guidelines, there is a statement that all 'measuring, weighing, recording and controlling equipment' should be calibrated at regular intervals and that this calibration should be recorded (Paragraph 3.41).

Similarly, there is a statement in the US Code of Federal Regulations that all 'automatic, mechanical or electronic equipment' shall have a written programme for calibration and that written records must be kept (CFR 211.68 (a)). Additionally, the FDA guide to inspection of computer systems in drug processing states that 'sensors should be systematically calibrated and checked for signal outputs'. The same document states that 'the accuracy and performance of these devices is vital'.

The newly revised Code of Practice for Qualified Persons (see Chapter 8 for more details), specifies that calibration records are one of the items that a QP must ensure are in existence before certifying a batch of product for release on to the marketplace.

11

Inspections and Auditing

11.1 Introduction

A major facet of the pharmaceutical industry is the process of inspections or auditing of facilities to ensure that they comply with all the requirements of the relevant standards, and that all necessary systems are in place.

In many cases, the words ‘inspection’ and ‘audit’ are used interchangeably. However, there is a difference between the two processes. An inspection is a one-way process in which a review is carried out and compliance (or otherwise) confirmed. There is no discussion on how improvements can be made. This process is generally used in the regulatory context. An audit, on the other hand, is a two-way process in which compliance (or otherwise) is reviewed and discussion takes place on how improvements can take place. This approach is more appropriate in the context of internal processes and consultancy situations. To prevent confusion, the term ‘inspection’ will be used throughout this chapter, apart from the section dealing with auditing of suppliers. However, in the majority of cases, the term ‘audit’ can be assumed to apply as well.

The chapter starts with a review of the different types of inspection in which companies become involved. There are internal ones, primarily the self-inspection programme but also, on occasions, independent quality assurance activities. From an external viewpoint, companies will receive inspections from regulatory authorities, from potential contract givers and possibly, from independent consultants. Additionally, they will carry out inspections of suppliers’ premises.

In a time when globalization of the industry is continuing apace, many companies are entering export markets and hence become involved in inspection requirements from other countries. In an effort to reduce the cost and time resources required for these activities, there are a growing number of mutual recognition activities developing around the world. The major ones are reviewed in this chapter.

Following on, there is a review of the particular skills that are required in order to prepare for and participate in inspections. These range from the technical aspects like

knowledge of the standards and of the facility to the more people-oriented issues relating to communication.

Finally, there is a discussion of the issues facing countries that are not yet in the mainstream of the pharmaceutical industry, but need to demonstrate that they can comply with current requirements in order to compete in the global marketplace.

11.2 Types of inspections

Companies that are manufacturing in the pharmaceutical industry become accustomed to being inspected on a regular basis, and also need to be able to organize and run inspections themselves. This section deals with the different types of inspection that a company will be involved with, either as the inspectee or as the inspector.

Inspections of manufacturing facilities tend to go through a number of stages, which together build towards a cohesive inspection programme. Starting from the base, there is the informal self-inspection that takes place on a daily basis by operators and managers alike. If something is seen to be wrong, it is immediately put right.

Next there is the formal self-inspection process that takes place on a regular basis, and is a specified requirement of GMP. The purpose of this is to take a step back from the day-to-day activities, to review for compliance to GMP and look for ways that the system can be improved. There may also be a need to conduct self-inspections as a result of a specific problem such as frequent complaints.

The next stage may or may not take place, depending on the size of the organization. It involves the use of QA staff as 'internal auditors' to review the system for compliance. In a smaller company, this step and the previous one tend to blend into one another.

Finally, there is the external inspection. This will come from a number of sources. There will obviously be the national regulatory inspections related to manufacturing authorizations and marketing authorizations. If a company is planning to export its products, there may be inspections from overseas inspectors. In addition, if a company is entering into a contract manufacturing relationship with one or more other companies, the inspectors from those companies will want to ensure that there is no risk to their products. Some companies also use consultants to support them in GMP improvement projects. In such a case, a GMP inspection, against the appropriate national or international standard, would be the first step to be carried out.

11.2.1 Internal inspections

For most companies, the internal inspection will be in the form of a self-inspection programme. This programme should include a written procedure detailing what is to be inspected and at what frequency. It should be used to ensure that a consistent approach is achieved.

The areas to be inspected would include (but would not necessarily be limited to): the personnel working in the facility; production and ancillary facilities; maintenance of the factory and plant; warehousing of all materials; manufacturing and testing equipment; production and in-process controls; quality control procedures; documentation preparation, use and compliance; sanitation and hygiene regimes; validation and monitoring

programmes; instrument calibration; recall procedures; handling of complaints; control of printed components; label control; purchasing; and follow-up to previous self-inspections. In other words, a complete review of all aspects of GMP.

The self-inspection team is appointed by the management of the company and is made up of a mixture of people, including experts in GMP and people familiar with the area in question. It is useful to have people from production, QC and engineering on the team, as they will bring different perspectives to the inspection.

It can also be a good training exercise to involve operators in the process. It is also possible to involve people from other parts of the company, or even outside the company, if it will add value to the process. It is important that the team members are encouraged to be objective in their evaluation.

The team leader needs to be someone who has access to the resources to produce a report at the end of the process, and with the authority and experience to organize and manage a team activity. Hence it is usually, but not always, a manager or supervisor. The leader should be from a different department to take a more impartial viewpoint.

The frequency with which self-inspections are carried out will be dependent on the company. For a small company that can cover all their operations in one inspection, a quarterly or six-monthly review might be sufficient. However, for a larger company that needs to split the inspection into a number of sections, a programme of monthly inspections, covering the whole factory in three to six months might be more appropriate.

All inspections need reports as an outcome; otherwise there is no formal record of the findings and recommendations. This report should be issued as quickly as possible while things are fresh in people's minds. It does not need to be an elaborate, wordy document that no one will read. A simple list of findings with recommendations for corrective action is sufficient. However, it is important that responsibility for action and a timeframe are agreed either during the inspection or soon after the report is issued.

An inspection on its own is unlikely to be particularly effective and it is important that the company management ensures that the follow-up actions are carried out to the agreed timetable.

As mentioned above, larger companies may have teams of auditors within the quality assurance department, whose responsibilities would be to inspect the various parts of the factory. These auditors will take part in self-inspection programmes, but may also conduct their own inspections. These latter inspections are on occasion used as 'dry-runs' in companies preparing for regulatory or other external inspections.

Whatever the objective of an internal inspection, it must be recognized as beneficial by all parties. See case study 1 in Section 11.6 for an example of a self-inspection programme that went astray.

11.2.2 External inspections

As discussed previously, there are a number of different reasons why a company is inspected by an external body. However, the main reason, and the one that is common to all companies, is the inspection by the regulatory authority that is carried out as part of the process of licensing the factory and approving the products for sale. Hence the majority of this section deals with this type of inspection.

Inspections by regulatory authorities take a number of different forms, depending on the purpose of the inspection, the length of time since the previous inspection and the inspection history of the company.

Regulatory inspections – routine

A routine inspection is a full review of all aspects of GMP within a facility. Routine inspections may be announced or unannounced, depending on the history of the company, previous inspections and the policy of the country.

It is appropriate under the following circumstances:

- When a new facility is opened.
- When a manufacturing authorization is due for renewal.
- If there have been significant changes, such as new product lines, modification to processes, or changes in key personnel or premises.
- If the company has a history of non-compliance to GMP.
- If an inspection has not been carried out within the past three to five years.

Regulatory inspections – concise

A concise inspection is the examination of limited aspects relating to GMP compliance within a facility. (In some countries, they are known as abbreviated inspections.) It also involves inspection of any significant changes that have taken place since the last inspection. Depending on national practice, a company would normally be warned in advance about a concise inspection.

A concise inspection is applicable under the following circumstances:

- Where a company has a good history of GMP compliance through routine inspections in the past.
- Where a sample of aspects can be taken as a good indication of the overall level of GMP compliance.

However, if the concise inspection uncovers evidence that the level of GMP compliance has fallen, it may be appropriate to carry out a full GMP inspection at some point in the near future.

Regulatory inspections – follow-up

A follow-up inspection is performed specifically to monitor the response to corrective actions arising from a previous inspection. The company would not necessarily know in advance about the follow-up inspection.

A follow-up inspection is not limited *only* to subjects of corrective actions, but to monitor the result of corrective actions. They are limited to specific GMP requirements that have not been observed or that have been inadequately implemented.

Depending on the nature of the work required, they could be carried out between six weeks and six months after the original inspection has taken place.

Regulatory inspections – special

There are a number of circumstances in which special inspections may be necessary. The company may or may not be aware in advance of the inspection, depending on the reason for it.

If there have been complaints about a specific product that suggest there may be defects, then a spot check can take place. If there has been a product recall, this can also trigger an inspection, as would adverse drug reactions.

In each of these three cases, the inspection would focus on the specific product or aspect of production that is suspect. It is unlikely that the company would be warned in advance in these cases.

If the company has made an application for a marketing authorization or an export licence/authorization, this may also trigger an inspection.

Finally, if a company has asked for advice on specific regulatory requirements, it may be necessary for the inspectors to visit before they can provide that advice.

Regulatory inspections – quality systems review

The purpose of a quality systems review is to describe the QA system. The quality manual is a document describing the quality system that includes the entire operational process, quality management and QA approach of the company.

This type of review is similar to that which is carried out when a company if applying for accreditation to ISO 9000. It is an approach that has been used by the FDA in their medical devices inspections and is currently being piloted in some of their medicinal products inspections. (See Chapter 3 for a full discussion of ISO 9000 quality systems and the FDA QSIT programme.)

Regulatory inspections – timetable

Although there may be ideal timetables that should be achieved for inspections, in practice there are a number of factors that influence the frequency: the type of inspection being undertaken; the number of inspectors available and their workload; the number of companies to be inspected; and the size of the company, for example, a large company with several major departments may be inspected in a number of stages covering the time period of the manufacturing licence.

An ideal timetable would be a visit every one to two years. This gives the inspectors sufficient information to ensure that the company is achieving GMP compliance. From the company's point of view, it is not too onerous in terms of preparation time.

In terms of the duration, this will again depend on a number of factors: the size of the company; the purpose of the visit; or the size of the inspectorate team.

Regulatory inspections – dealing with problems

The powers that an inspectorate has to deal with unsatisfactory situations are controlled by national legislation. These powers often include:

- Suspension or revoking of the marketing authorization.
- Delay in approval of licences or marketing authorizations.
- Delay in the issue of a GMP certificate.
- Closure of a facility (only used in an extreme case where failure of a system or process has been identified, which presents a significant risk to the patient).
- Initiation of a product recall.

Differences between European and US regulatory inspections

Although the principles on inspection are the same for all regulatory bodies, there are some key differences between those carried out by European inspectors and those carried out by the FDA. Both focus on the quality, safety and efficacy of the product. However, whilst the European inspectors check for compliance to EU guidelines, the FDA inspectors require compliance to codes of federal regulations (CFRs). The European approach focuses on future activities and the facility, whilst the FDA approach focuses on past activities, primarily in documentation. European inspectors are experienced practitioners from industry, whilst FDA inspectors are trained to the role and do not have industry experience. Reports from European inspections are confidential, whilst those in USA are covered by the Freedom of Information Act and can be obtained on request.

11.2.3 Suppliers

Within the EU code of GMP, it states that materials should only be purchased from approved suppliers and that all aspects of the manufacture and distribution of materials should be reviewed with the supplier and with the manufacturer, if they are not one and the same company. By implication, this means that, wherever possible, an audit of the suppliers' premises should be carried out as part of the approval process.

A supplier audit will involve more than one function within the company. The process will generally be lead by the quality assurance department, but will also concern the purchasing department, as well as production and possibly engineering, depending on the material being purchased. Not all these departments need to be represented during the audit, but all should be involved in the preparatory work and the decision on whether to approve the supplier or not.

Many companies have a long-established list of suppliers, many of whom will not have been audited in the past. If this were the case, then the first step in preparing for an audit would be to review the history of the relationship between the company and the supplier. What is their performance on deliveries, in terms of accuracy and timeliness? How does the material perform during processing; does it cause problems within production? What other information is already on file about the supplier?

For a potential new supplier, there is less information available, although analysis of a sample of material to ensure it complies with the purchase specification should be a first step.

In either case, it is useful to send the supplier a pre-audit questionnaire, to be completed in advance of the visit. From experience, it is better to keep this questionnaire to just a few pages and to provide it to the supplier at least one month before the date of the audit, in order to guarantee receiving the completed form in good time.

When carrying out the audit, the team should focus on any major issues highlighted by the questionnaire, but also review the systems and premises against requirements of GMP. This would also be an opportunity to review any problems experienced with previous deliveries (in the case of an existing supplier) and to confirm details of the purchase specification. It is worth remembering that the suppliers are the experts in relation to their materials and that they might have constructive input to make into development of the specifications.

Once a supplier has been approved, it will be necessary to monitor their performance over time and occasionally revisit the premises. However, it is unlikely that an annual visit will be required, as would be expected for regulatory inspections of manufacturers' facilities.

11.2.4 Approaches to inspections

Irrespective of the purpose of the inspection, there are a number of approaches that can be taken by the inspectors. The end result will tend to be the same; it is the way of achieving it that differs. These approaches are reviewed below:

Process inspections

This is an inspection that reviews the processes running through the factory, independent of specific products. It includes a review of documentation (how it is issued and controlled), measurement (methods and calibration), manufacturing processes (planning, procedures, validation, deviations and traceability), distribution systems, reject control and corrective actions.

Product inspections

This is an inspection in which one or more products are examined in detail. It includes a review of design, development, change control, documentation, compliance, process control, quality control, complaints, packaging, stability and validation.

Systems inspections

This is an inspection in which the quality systems of the company are reviewed to see whether they are appropriate and whether they are being complied with.

General themes

Whichever approach is used, there are a number of questions that can be addressed:

- What should be happening, i.e. what is required?
- What is the described procedure, i.e. what has been planned?
- What is taking place in practice, i.e. what is happening?
- How does the plan compare with the requirement, i.e. does the standard need to be amended?
- How does the actual practice compare with the plan, i.e. does the performance need to be amended?

11.3 Mutual recognition of inspections

Whilst all good pharmaceutical manufacturers recognize the importance of inspections as part of the continuing quality assurance programme for the company, it is true to say that the preparation for and participation in a full inspection is a time-consuming and resource-intensive activity. For companies that are operating as contract manufacturers for multiple principals (companies giving contracts), it can become almost a full-time occupation for certain members of the team.

For companies that are exporting to a number of different countries, it would be disadvantageous to have to satisfy different sets of inspectors from each of the different countries. Fortunately, there are a number of mutual recognition agreements in place that make the situation more manageable. These agreements are intended to reduce the need for foreign inspectors from importing companies having to re-inspect facilities that have already been approved by their own regulatory authorities. Additionally, it should reduce the requirement for full retesting of finished products once they have been imported into a country.

In addition to the benefits coming from mutual recognition in terms of inspections and analysis, it is also a great benefit that harmonization of standards in general are being worked towards. The discussions on GMP in Chapter 4 show that the current situation is still quite diverse. A single global set of standards is some way off. However, as shown in this section, there are a number of processes under way that are moving us in this direction.

11.3.1 PIC/S

PIC/S stands for the Pharmaceutical Inspection Convention and the Pharmaceutical Inspection Co-operation Scheme, which are a pair of international agreements that operate together.

Pharmaceutical Inspection Convention (PIC)

PIC was set up in 1970 under the auspices of the European Free Trade Association. Its full title was 'The Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmaceutical Products'.

The purpose of PIC was as follows:

- To establish mutual recognition of inspections between member countries.
- To bring about harmonization in GMP standards.
- To ensure that equivalent inspection methodology was used in the member countries.
- To provide a mechanism for training of inspectors.
- To set up a forum for the exchange of information between inspectors and inspectorates in the member countries.
- To allow member countries to have mutual confidence in the results of inspections carried out by inspectors in other countries.

In other words, if a company was planning to export product to another country within PIC, the inspectorate of the importing country would not necessarily have to carry out an inspection of the exporter, if a satisfactory inspection history by the national inspectorate was in existence.

PIC is a legally binding treaty between countries. The original signatories were: Austria, Denmark, Finland, Iceland, Liechtenstein, Norway, Portugal, Sweden, Switzerland and UK (these being the members of EFTA in 1970). Subsequently Hungary, Ireland, Romania, Germany, Italy, Belgium, France and Australia signed up to PIC between 1971 and 1993. At this point, it became clear that there was a legal problem that required a change of strategy.

Pharmaceutical Inspection Co-operation Scheme (PIC Scheme)

Under EU law, it is not permissible for individual Member States to sign treaties with countries outside the EU. Only the European Commission can sign such treaties. However, the European Commission is not a member of PIC. If the work of PIC was not to be lost, a compromise needed to be found.

The PIC Scheme was set up in 1995. It differs from PIC in that it is an informal agreement between regulatory authorities in Member States and is not legally binding. However, its goals are an extension of those of PIC, as shown below (taken from the PIC/S website):

- To pursue and strengthen the co-operation established between the participating authorities in the field of inspection and related areas, with a view to maintaining the mutual confidence and promoting quality assurance of inspections.
- To provide the framework for all necessary exchange of information and experience.
- To co-ordinate mutual training for inspectors and other technical experts in related fields.
- To continue common efforts towards the improvement and harmonization of technical standards and procedures regarding the inspection of the manufacture of medicinal products and the testing of medicinal products by official control laboratories.
- To continue common efforts for the development, harmonization and maintenance of GMP.
- To extend the co-operation of other competent authorities having the national arrangements necessary to apply equivalent standards and procedures with a view to contributing to global harmonization.

Since 1995, the Netherlands, the Czech Republic, the Slovak Republic, Spain, Canada and Singapore have joined the PIC Scheme. All the original members of PIC have acceded to the PIC Scheme. There are thus 24 regulatory bodies taking part in the PIC Scheme and the same 24 regulatory bodies taking part in the joint operation of PIC/S.

Principal activities of PIC/S

On at least a six-monthly basis, representatives of all the member regulatory bodies meet together to promote and carry forward the goals of the PIC Scheme, by organizing seminars and other activities.

An annual training seminar is organized for inspectors from the member countries. Countries that are considering joining PIC/S and other interested parties may attend these seminars as observers. Each seminar takes a specific aspect of GMP as its theme. The outcome of the seminar will usually be the setting up of a working party to draft out documentation on the theme, which will be published by PIC/S at a later date.

Training of inspectors within PIC/S is enhanced by the organization of joint visits where inspectors from three different countries carry out inspections in teams in each of the three countries. Apart from a useful training exercise, this is also a good way of highlighting any differences in inspection practices between member countries.

A number of ‘Expert Circles’ have been set up as special interest groups to facilitate exchange of experiences and knowledge on particular topics. These circles meet at least annually and develop new documentation on the topics in question.

The publication of documentation is a major activity within PIC/S. These documents are in a number of forms: guidelines, guidance documents, recommendations, explanatory

notes and *aides-memoire*. In addition, the proceedings of seminars are published. Details of all these documents, and more information about PIC/S can be found on the website (see Bibliography for details.)

In order to become a member of the PIC Scheme, countries must be able to demonstrate that they have an effective licensing and inspection system that is at least comparable with the standard achieved by other PIC/S members. A detailed assessment is made by current members before an application is approved, including a review of the systems in place and observations of inspections being carried out in practice.

11.3.2 Mutual recognition between PIC/S and EMEA

Whilst 13 of the 15 member states of the EU are participants in PIC/S (with Luxembourg and Greece being the non-participants), there is no official relationship between PIC/S and EU. The main regulatory body for the EU is the European Medicines Evaluation Agency. Consultation procedures between PIC/S and EMEA are in the process of being harmonized and EMEA attends PIC/S meetings as an observer.

11.3.3 Mutual recognition between Europe and North America

Although Canada is a member of PIC/S, the USA is not. However, mutual recognition programmes are being pursued between Europe and North America.

Agreement on recognition was reached with Canada in the latter part of 2000. This agreement has some restrictions because, in Canada, factories producing product solely for export are not subject to the requirement for a regulatory inspection and issuing of a manufacturing licence. However, assuming that the company has waived this exemption and has been inspected by the Canadian authorities, there is no need for an EU inspector to visit the factory.

The terms of a mutual recognition agreement between Europe and the USA have been drafted and are currently in the evaluation stage. This stage is scheduled for completion by 2002. Once the agreement comes into force, a three-year transition period will begin.

11.3.4 Mutual recognition between Europe and other countries

On 1 January 1999, a mutual recognition agreement came into force between the EU and Australia. For human medicines, there is no transition period, although for veterinary products, there is a two-year transition. On the same date, a similar agreement came into force between the EU and New Zealand. Once again, there is a transition period, this time of three years, for veterinary products, but none for human medicines.

A mutual recognition agreement was signed in 1999 between the EU and Switzerland, and is effective from early 2001.

11.3.5 International Conference on Harmonisation

The full title of ICH is The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use**.** ICH is not primarily involved in the organization, monitoring or operation of inspections. However, since it is a major player in the move towards the harmonization of standards, it is important to review its purpose and activities briefly here.

ICH was set up in 1990 as a joint forum between regulatory authorities and the pharmaceutical industry, with a focus on testing procedures to monitor the safety, quality and efficacy of medicines. The mission of ICH is as follows:

> The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. The objective of such harmonisation is a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health. (ICH Terms of Reference)

The emphasis was on products containing new drugs and the scope of the activities is limited to registrations in Western Europe, Japan and the USA, where the majority of the work on new chemical entities is carried out.

Members of ICH

The founder members of ICH have become the permanent members. They represent the regulatory authorities and the national industry bodies for each of the three regions:

- The European Commission represents the regulatory authorities of the member states of the EU. Administratively, the ICH activities are co-ordinated via EMEA.
- The European Federation of Pharmaceutical Industries' Associations (EFPIA) represents the individual associations from 16 countries within Western Europe.
- The Ministry of Health and Welfare (Japan) has the brief for public health, amongst other things, in Japan. The Pharmaceutical and Cosmetics Division of the Pharmaceutical Affairs Bureau is responsible for ICH activities.
- The Japan Pharmaceutical Manufacturers Association (JPMA) represents the 90 manufacturing companies within the Japanese industry.
- The Food and Drug Administration is the regulatory authority for the USA. ICH activities are co-ordinated between the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research.
- The Pharmaceutical Research and Manufacturers of America (PhRMA) was formally known as the Pharmaceutical Manufacturers Association (PMA). It represents the research-based section of the pharmaceutical industry in the USA.

In order to ensure that ICH maintains a link with countries outside of the three main regions, there are a number of observers to the process, who have permanent seats on the ICH Steering Committee.

- The World Health Organization, which deals primarily with countries in the developing world or where the industry is just emerging.
- The European Free Trade Association, which provides a link back to PIC/S.
- Canada, via the Drugs Directorate, Health Canada.

Finally, there is an important role within ICH for the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), which represents the global research industry. This is the main link to countries outside of the three regions. IFPMA provides support to ICH by running the secretariat.

Activities of ICH

At the initial meeting of ICH in 1990, 11 topics were identified for harmonization work, divided into three main themes of quality, safety and efficacy. Each topic became the subject of an expert working group. The process that takes place in order to achieve harmonization has a number of distinct steps as follows.

Step 1: Consensus building. During this step, draft documents are prepared and consensus sought between all the members. Once this technical consensus is achieved, the draft is signed off by the expert working group.
Step 2: Start of regulatory action. At this point, consultation is extended to include the regulatory authorities.
Step 3: Regulatory consultation (outside of the ICH forum). The document is issued as a draft CPMP guideline within the EU; as draft guidance in the Federal Register in the USA; and in Japan it is subject to internal and external consultation. The three authorities liaise in order to come to a joint final document. At this point, regulatory authorities from outside ICH can also comment.
Step 4: Adoption of a tripartite harmonized text. Assuming that the text has not been significantly amended during the consultation period, the document is then adopted by the ICH Steering Committee.
Step 5: Implementation (outside the ICH forum). The document is implemented via the normal routes within each of the countries in the three regions.

In 1997, it was determined that phase 1 of the ICH activities had been successfully completed. It continues to operate in phase 2 as a tool to maintain the dialogue between the various parties and prevent divergence of technical requirements in the future. More information on ICH can be obtained via their website (see the Bibliography for details).

11.3.6 The WHO certification scheme

There are many companies in countries that are not members of PIC/S and yet wish to either export or import finished products. In the former case, they need to be able to convince the regulatory authorities in the importing country that their products are safe, efficacious and manufactured in compliance with all GMP requirements. In the latter case,

they need assurance that the product being brought into the country is satisfactory in the same way. However, the time and money required to arrange inspections is not always available.

The WHO certification scheme was set up to facilitate these situations. The full title of the scheme is 'The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce'. The scheme was originally proposed in 1969, amended in 1975 and 1988, and published in its current form in 1996.

The scheme is essentially an administrative tool that may be used by any Member State of the United Nations who wishes to register for the scheme. All members can use the scheme to monitor the quality of imports. However, if a Member State wishes to use the scheme to facilitate exports, they must be able to demonstrate compliance with a number of requirements as follows.

- There must be a licensing framework in place that covers not only the authorization of products, but also the manufacturers and distributors working within the industry.
- There must be a national GMP code in place, at least equivalent to the WHO requirements and it must be enforced across the country. (Adoption of appropriate international guidelines such as the EU guide would be an acceptable alternative.)
- There must be a system of quality control for finished products produced within the country, including an independent quality control laboratory.
- There must be a competent national inspectorate, which is part of the regulatory authority, and which has the knowledge, experience, resources and authority to reinforce the GMP requirements across the industry.
- There must be resources available to administer the scheme within the country. This will involve issuing of certificates, and monitoring the scheme to ensure that it is operating correctly and that any quality problems are highlighted immediately.

The WHO scheme relates to specific products rather than to the whole operation of any one manufacturer. When an interested party from the importing country initiates an enquiry regarding a particular product, the regulatory authority of the exporting country issues a certificate to the following effect:

- The product has a marketing authorization within the country of export, or if not, the reasons why not.
- The manufacturing facility in which the product is produced is inspected regularly by the national regulatory inspectors and has been demonstrated to achieve GMP compliance.
- The product documentation, including labelling, is authorized in the exporting country.

Three different types of certificate can be issued, depending on the circumstances:

- Certificate of a pharmaceutical product: this is used when a product licence has been applied for and it is proposed that a regular importation arrangement is to be set up.
- Statement of licensing status: this is used during an international tendering process.
- Batch certificate: this relates to the importation of a specific batch of product and, unlike the previous two, which are issued by the regulatory authority, this certificate is normally issued by the exporting company itself.

11.4 Guidance on participating in inspections

Participating in an inspection, either as an inspector or an inspectee, requires a certain level of knowledge and experience in a variety of different areas. Obviously, it is important to have a detailed understanding of the standards against which the facility is being inspected.

Secondly, it is critical that the representative of the inspectee knows the facility well and is able to answer the majority of the questions accurately. For the inspector, it is helpful and will increase the effectiveness of the inspection if sufficient preparation has been carried out to ensure at least a basic knowledge of the facility.

Thirdly, inspections are exercises in communication. The interaction between the various parties will affect how the inspection proceeds and will determine whether it is an effective one or not. Hence there is an aspect of personal interaction, which is very important but is often forgotten in the process of training inspectors.

Finally, there is the actual process of carrying out an inspection: how to prepare effectively; how to carry out the inspection effectively; and how to ensure effective follow-up. Each of these aspects is addressed separately within this section. The section is written both from the viewpoint of the inspector and the inspectee, but inevitably, the emphasis will be on the former role. However, bearing in mind that all companies need to carry out their own internal inspections and supplier audits as a minimum, there are many instances where company personnel will have to carry out the role of inspectors and hence there should be something for everyone in the following notes.

11.4.1 Inspection guidelines

There are a number of sources of guidance for inspectors, in relation to the first area of knowledge – the technical aspects. Obviously, there are the source documents – the various GMP guidelines and regulatory documents. However, there are also some documents written specifically about the inspection process that might be useful, particularly for relatively new inspectors.

PIC/S

As discussed previously in this chapter, PIC/S issues documents on a variety of topics. Whilst these documents are primarily intended for the guidance of inspectorates, they are useful documents for companies with regard to questions of implementation. All these documents are listed on the website and many can be downloaded free of charge (see the Bibliography for details of the PIC/S website).

FDA

The FDA has over the years published a series of guides to inspections. Whilst primarily intended to support the activities of the FDA inspectors, they are freely available and can be downloaded from the FDA website (see the Bibliography for details of the website). They are particularly useful in preparing for an FDA inspection, but can also be helpful

for companies who are developing activities in a particular area. The guides to inspections are as follows:

- Bulk pharmaceutical chemicals, September 1991
- High purity water systems, July 1993
- Lyophilization of parenterals, July 1993
- Pharmaceutical quality control laboratories, July 1993
- Microbiological pharmaceutical quality control laboratories, July 1993
- Validation of cleaning processes, July 1993
- Dosage form drug manufacturers – cGMPs, October 1993
- Oral solid dosage forms pre/post-approval issues, January 1994
- Topical drug products, July 1994
- Oral solutions and suspensions, August 1994

In addition, the FDA publishes guides to inspections in topics related to biotechnology, biologicals, computer issues (although the main reference document has not been updated since 1983) and devices. Also published and freely available are the *FDA Investigations Operations Manual* and *International Inspection Manual and Travel Guide*. These are a combination of technical and administrative items. Finally, there is a long list of *Inspector's Technical Guides*; however, once again, many of the documents were written more than 20 years ago and hence their relevance must be reviewed in each individual case.

WHO

In 1992, the WHO published a document entitled 'Provisional guidelines on the inspection of pharmaceutical manufacturers'. The intention was to harmonize the activities of inspectorates in the developing world and the document was aimed primarily at regulatory inspectors. However, they are also useful for manufacturing companies, both as a preparation for an external inspection and as a reference text for the planning of internal inspection programmes.

The guidelines are applicable mainly to the manufacture of secondary pharmaceuticals and to active pharmaceutical ingredients, but may also be applied to the inspection of facilities for the production of other products, which may be covered by national legislation in some companies. Examples of these products would include: biologicals, medical devices, diagnostics or food.

Since competent inspection of manufacturing facilities is a key element of the WHO certification scheme discussed above, this guideline should certainly be used by any country that is registered to export under that scheme. However, additionally, it may be useful in planning and carrying out inspections of quality systems against ISO 9000 (see Chapter 3) or for supplier audits.

The guidelines cover both the process of carrying out an inspection and the technical content thereof. They start with a review of the role of the inspector. (This topic is discussed in more detail later in the chapter.) Next there is an overview of the different types of inspections. (These were covered in an earlier section of the chapter.) Next there is a discussion on preparing for an inspection. Finally, there is a review of how the inspection should be conducted, what to look out for, how to write the report and the regulatory actions open to an inspector who finds an unsatisfactory situation in existence.

11.4.2 Developing knowledge of the facility

Knowledge of the individual facility will be different in every case and can only be dealt with on a case-by-case basis, although some suggestions are made in this section.

From the point of view of the company that is being audited, it would be easy to assume that someone who is very familiar with the facility and its systems would be delegated to accompany the inspector throughout the visit. This person would not necessarily be able to answer all the questions themselves, but they would know whom to contact to find the answers. However, from experience, this is not always the approach taken by companies, particularly those that are not used to the inspection process. See case study 2 for an example of how *not* to deal with a regulatory inspector.

From the point of view of inspectors, it is obviously not likely that they will know the facility very well, unless they have visited it many times. However, any information that can be obtained during the preparation stage is likely to increase the effectiveness of the inspection process.

For an initial inspection, there are a number of potential sources of information about the company. If it is a regulatory inspection, then the application dossier will include information about the company, including a site master file. For an inspection by a non-regulatory inspection (such as in a potential contract manufacturing situation) the company should be asked to complete a pre-inspection questionnaire and/or provide layout diagrams. Sufficient time should always be allowed for these to be provided; it would be no good asking for them two days before the inspection is due to take place.

Any documentation such as manuals and procedures can also give an overview of the company for the inspector. This will depend on company policy – some companies treat all such documents as confidential and do not allow them to leave the site. (However, in the case of ISO 9000 certification inspections, provision of the quality manual and procedures is a prerequisite to setting up the inspection in the first place.)

The annual report, if the company is required to produce one, is a useful background document. Whilst this rarely has any technical detail, it helps to provide a full overview of the company.

Where an inspection is not the first one to be carried out in a company, there will be a certain amount of information that should be available to the inspector, whether a representative of a regulatory body or someone carrying out an inspection for a private company. There should be a company file, which will contain information obtained prior to or during other visits. However, it is important to be aware that this information may not be completely up to date. If the company produces a site master file, this will also be a useful document.

Specifically for regulatory inspections, information is also available from the site manufacturing licence and from the registration dossiers submitted for the products being manufactured. A further source of information is monitoring data, not just of inspections, but also of any recalls, complaints or product testing.

A visit to a company should always start with a review of progress against recommendations made during the last inspection. Hence it is important that the inspector is fully familiar with this material.

11.4.3 Inspections – an exercise in communications

Inspections are a snapshot in time. They are relatively short by nature – it is unlikely that an inspection will be more than five days long, unless the manufacturing facility is very large. Hence it is important for the time to be used effectively. From the point of view of the inspector, it is necessary to obtain as much information as possible, together with the evidence to back up that information. From the point of view of the inspectee, it is important to be able to put across the point of view of the company, explain any problems and justify any approaches that appear unusual to the inspector. Hence this is an exercise in communications, and two-way communications at that.

The role of the inspector

There are a number of different approaches that can be taken by an inspector, which will affect how the inspection is carried out. The one that is most appropriate will depend on the nature of the inspection, the relationship between the inspector and the inspectee, and the history of previous inspections.

The primary role of an inspector must be as an observer of facts. It is a key responsibility to report factually on the standards being achieved within the factory. This can be termed as a policing role. It will be the main approach that will be taken by a regulatory inspector and will also be appropriate in initial inspections by other external bodies. It would be less appropriate in the case of a self-inspection activity.

However, there are many occasions when an inspector takes the role of an advisor or coach, and uses the opportunity of the inspection to suggest ways of improving manufacture or control. The company may also see the inspection as an opportunity to seek support and guidance in particular areas where compliance is in question. This is particularly appropriate in situations where there is a business relationship between the inspector and the inspectee (see case study 3 for an example of this approach).

In the past, regulatory inspectors were reluctant to provide advice to companies on topics such as the design of new buildings, in case any such advice was taken as a tacit approval of one particular approach over another. However, this view has now changed, and inspectors are more willing to review plans whilst they are still on the drawing board, rather than waiting until the building is complete and it is too late to make major changes. It must be stressed, however, that this approach must always be made within the context of national policy.

There are a few circumstances in which the inspector and the inspectee can take a partnership approach to the process of inspections. This is particularly appropriate in the case of supplier audits, where co-operation on improvement of a specific process can produce a win–win situation between the two parties. This would also be the case where an independent consultant is working with a company to help them improve their GMP compliance.

The inspector as communicator

In order to be able to communicate effectively, it is important to use the language that is most appropriate to the level being addressed. An inspector will meet and may have to deal with many people within a company from members of the board to the shop floor operators, and good inspectors are able to both give and receive information on all occasions – and to recognize where it is most appropriate to ask particular questions. For

example, a board member or senior manager would be able to answer questions about investments and company policies, but in order to determine the answers to technical questions such as 'how is this process carried out', the inspector will be more likely to talk to someone in the production area, such as the supervisor or the operator.

It is important that both the inspector and the company representatives be aware of their body language. If the inspector asks a question (particularly if it is a difficult one), then it is important to be interested in the answer. Looking around or paying attention to something else would only increase the nervousness or the irritation of the person making the reply. Both parties should try to keep their arms open, rather than crossed. This indicates receptiveness to the discussion in progress, rather than defensiveness or aggression.

It is necessary for an inspector to be aware of and sensitive to the company culture in relation to visitors. It may be perfectly acceptable to talk directly to people encountered during the factory visit but, in some companies, it is preferred that questions are addressed through the company representative.

In the case of a regulatory inspector, there is always the right to insist on talking to anyone and seeing anything. In the interest of establishing or maintaining a good relationship with the company, doing things the way the company would prefer tends to be the preferred approach. However, this would only be valid if it does not create a barrier to obtaining answers. It may be necessary to find ways around the company culture if this happens.

For inspectors working outside their own country, it is important to remember that different countries have different cultures and social behaviour that need to be recognized and taken into account. On occasion, this can have a major impact on the effectiveness of communications.

Effective inspectors would always be aware of the potential or perceived impact of their actions, particularly in a situation where there are major non-compliance issues. It is their role independently to observe and report the facts. People in the company may have concerns about the outcome of the inspection that may be unjustified, but which could be caused by the inspector's behaviour. This would have an effect on communications and would reduce the likelihood that the company representatives will be open in their answers.

One of the biggest barriers to effective communications is a misunderstanding over the purpose of those communications. A full understanding and agreement on the objectives of the inspection both in the planning stage and at the start of the inspection is critical.

Relieving the stress of an inspection

An inspection is a stressful situation for both parties. This will tend to affect the way people behave. A recognition of some typical behaviours and how to avoid the negative effects is a useful addition to the tool bag of both inspectors and inspectees.

All discussions should be held on a factual basis. Inspectors should collect the evidence in all situations, and company representatives should be happy to provide it. There should be no discussions that become personal and that descend to accusations. A considered comment after the event would be more effective than comments made in the heat of the moment.

It is always important to remain polite, even if the other party becomes rude (and from experience, this will happen on occasion, particularly if they feel they are being accused of something). The more professional an approach both parties make to an inspection, the more relaxed they will be and the more effective the whole process will be. This can only

help to make the inspection proceed more successfully. The key to a professional approach is preparation. The inspector will have a full agenda prepared and be aware of the key issues to be reviewed. Equally, the company that prepares well for an inspection will be a company that comes across as a more professional one to the inspector.

It is important that an inspector maintains a consistent approach to a company, both within a single inspection and from one inspection to another. Companies need to know where they stand on the various issues that are likely to arise.

Inspectors should check that any questions or requests are made clearly and that they are understood. Similarly, inspectees should ensure that their responses and explanations are fully understood. Just because a speaker understands what they are saying, they should never assume that everyone else will. Becoming impatient with someone who misunderstands a question or a response will not help the situation, it will only make people more nervous.

This point is particularly critical for inspectors who are working overseas via an interpreter or with people whose first language is not the same as their own. It may be necessary to ask a question more than once, in different ways to ensure that it has been understood. From experience, it is also necessary to check back on answers received, in order to ensure that what has been said and translated is what was actually meant.

Integrity is a critical part of all communications, particularly in a situation like a regulatory inspection. Decisions that inspectors make can have a significant effect on the business performance of the companies being inspected. Hence, it is important that the inspector's reputation is above question at all times.

Both parties should remain tactful and diplomatic at all times. An antagonistic attitude should not be allowed to cause provocation. In all cases, the objective is to collect evidence, not to have an argument about it.

As has been mentioned several times before, an inspection, whilst an essential part of running a pharmaceutical company, is also a resource-intensive activity, both before and during the inspection itself. It is important that both parties, but particularly the inspector, contribute to the effectiveness of the process by being well prepared, clear and direct in questions and discussions.

Maintaining independence as an inspector

This section has dealt with the process of successful communications and their importance in carrying out an effective inspection. However, it is important to conclude by emphasizing the independence of the inspector. Above all, inspectors have a responsibility to ensure that the evidence assembled is true and accurate. It is necessary to be rigorous in investigations and not look only at the parts that the company wants the inspector to examine. After all, it is unlikely that a company will volunteer information about their problem areas, even in a situation where an excellent relationship exists between the inspector and the inspectee.

11.4.4 Preparing for and conducting an inspection

Apart from the technical aspects of an inspection, and the importance of developing effective relationships with the people being dealt with, it is also important that an inspector is equipped with the skills to handle the mechanics of an inspection; from the

preparation, through the inspection itself to the report and follow-up actions. There are no regulations or guidelines for this, although the WHO guide mentioned above has some suggestions. The following suggestions are taken from the author's experiences over more than ten years and dozens of company inspections.

Preparing for an inspection

The first step in preparation is to define the purpose and scope of the inspection. There are a number of different types of inspection, as discussed earlier. However, it is also necessary to decide whether the inspection will cover the entire facility or just part of it. For example, if a company produces a range of dosage types such as liquids, tablets and sterile products, it may be preferable to take one area at a time, rather than covering everything in one go.

Once the purpose of the inspection and its depth has been decided upon, it is then necessary to decide how much time will be required to carry it out. It is also appropriate at this point to decide when the inspection will take place. Whether this is done in conjunction with the company in question will depend on whether it is to be an announced or unannounced inspection. For regulatory inspections, this will depend on the objective of the inspection and the accepted practice within the inspectorate. For all other types of inspections, it is unlikely that they would be unannounced.

Some inspections are carried out by one person, whilst others are carried out by a team of inspectors. From experience, a team approach is preferable if possible, since it allows the workload to be split, increases the range of knowledge and expertise of the inspectors, and provides a 'sounding board' for the development of observations.

Once the timing of the inspection is finalized, there will be a number of people who need to be notified. These will include the company (in the case of an announced inspection), the members of the inspection team and other interested parties, such as the administrators who organize travel arrangements.

In the case of a regulatory inspection, there may be other sections of the authority that have dealings with the company and may need to be informed. If such an inspection is to be undertaken in other countries, the regulatory authorities of those countries would be informed as a matter of courtesy.

Conducting the inspection

During the preparation stage, one of the items to have been prepared will be a draft programme for the inspection. Whilst every inspection will be different in the detail, there are some standard items that can be included in all of them:

All inspections should start with an opening meeting to ensure everyone has been briefed on the purpose of the inspections and that the objectives are understood.

- A request should have been made for any help that will be needed by the inspectors, including the provision of technical officers to accompany them during their visit.
- It is useful to have an orientation tour of the plant, particularly if it is the first visit the inspectors have made. However, they should remember that this is an initial walk-through only and not be pulled into detailed discussions at this point.

Once the introductions have been completed, it is time to begin the main activity of the inspection – the fact-finding to assess compliance to GMP. Periodically, it is necessary to review the programme and see whether it needs to be revised in the light of the

information that has been obtained so far. That is why the original agenda is never more than a draft. From experience, most inspections throw up surprises that necessitate a change of emphasis. The inspection then continues using the revised plan. It is important to make the management of the company aware of any changes, so that they can amend their plans accordingly.

There are three main approaches that can be used to carry out an inspection:

- To trace forward is to start at goods inwards and to follow the system through the factory logically to the dispatch warehouse at the end. This will tend to be a hypothetical exercise that concentrates on the physical systems.
- To trace backwards is to take a pack of finished product off the shelf in the warehouse and review its entire history back through the system. This will be a fact-based exercise that concentrates on documentation.
- The random approach is to start from points around the factory that appear to be significant – and see where they lead. This approach is probably not a recommended one for an inexperienced inspector.

The choice of method will depend on the purpose of the inspection, the previous inspection history of the company, and the personal choice of the inspector.

In eliciting facts from people, it is important to ask questions in a way that will lead to an appropriate response. For this reason, closed questions, which lead to a 'yes' or 'no' answer are much less useful than open questions that lead to explanations. For example 'Is there a procedure for this operation?' will tend to bring out far less information than 'Can you talk me through the procedure for this operation?'.

One of the key skills needed for a successful inspection is that of note taking. There is no point in asking all the right questions if, at the end of the inspection, there is no accurate record of the answers. This is one of the advantages of the team approach to inspections. Whilst one person is talking, the other can record. However, when the inspection is carried out by an individual, it is necessary to ask the questions and record the responses.

There are a few key points to be remembered when taking notes:

- It is important to record all the relevant facts at the appropriate level of detail. Facts should always be verified, not taken on trust or based on assumptions.
- Records should be of specific information, not general impressions.
- Details should be recorded as they are seen, not as the company says they should be.
- Accuracy is paramount. There is nothing that undermines the credibility and authority of an inspector more than being proved wrong, particularly in front of senior management.
- The notes can be made in an open manner. The results of the inspection will be the subject of a report, so there is no secret that needs to be hidden.

There are a number of specific ways in which records can be made. The chosen one will be a combination of what is most appropriate at the time and personal choice. Each method has advantages and disadvantages:

- Many inspectors take detailed but rough notes that can be reviewed and tidied up later. This allows them to concentrate on the discussion. However, it involves extra work outside of the daily inspection programme.

- Checklists are a detailed, but structured way of taking notes. They are a good way of ensuring that all topics are covered and hence may be useful, in particular for inexperienced inspectors. However, they are inevitably made up of closed questions and can stifle further discussion if not used flexibly.
- Flow-charts can be a good way for the inspectors to check their understanding of an operation and how it fits into the overall system.
- A tape recorder has been used by inspectors in the past. However, this may be off-putting for the person being interviewed as it makes the inspector seem more remote.
- A video camera is useful for recording information about the plant and premises, but will be of little use in obtaining information, as it will prevent people from relaxing and answering questions sensibly.
- A still camera may also be useful for recording information about the plant or premises. (It should be noted that, for both the camera and the video, permission might need to be obtained from the company before they can be used, unless, in the case of a regulatory inspection, national legislation provides the inspector with the authority to use such equipment.)

Where the inspection has been carried out by a team, there needs to be some time at the end of the visit for the inspectors to review their findings in advance of the closing meeting. This is particularly so when members of the team have been visiting different parts of the site at the same time.

The first step is to pool non-compliances so that the whole team has the same set of information. The non-compliances are then categorized into critical, major, minor or some similar system. Depending on the number of non-compliances identified, it may not be possible or advisable to cover all of them in the closing meeting. In this case, they can be ranked in order of priority so that the key issues can be discussed. It is also important to anticipate what questions might be raised in the meeting and have the answers ready; this is particularly true if there are likely to be any contentious issues.

The last activity at the company is the closing meeting with the management team to give an initial feedback of findings. This meeting has two main objectives:

- It is an opportunity for the management team to learn from the inspector. Companies often widen the audience for these meetings to more than the immediate technical team.
- It ensures that there will be no surprises in the report. The bad news (and the good news) will be reviewed and clarified on the spot.

From experience, there is sometimes a third objective, in the case of non-regulatory inspections. In a company, particularly a small one, where the technical management have had difficulty convincing the financial managers that significant investment in the factory is required to achieve GMP, the closing meeting is used to add weight to the argument, by adding the opinion of an independent, external body.

Inspection reports

The final output of an inspection is a written report on the findings. For non-regulatory inspections, this will often include recommendations for improvements in levels of compliance. In the case of regulatory inspections, the non-conformance is highlighted, but

it is generally left to the company to respond and say how they intend to overcome the problem. In all cases, there should be a timeframe for a required response.

The WHO guideline on inspections mentioned previously provides an example of the type of report that can be written after an inspection. The report is split into four parts as described below.

- General information about the company can be taken directly from the information provided by the company itself, provided it is annotated as such and verified during the inspection.
- The description of the inspection lists all the parts of the factory that have been inspected.
- The next part is devoted to observations, either negative or positive, including any major changes that have taken place since the previous visit. Negative observations should differentiate between poor systems and failure to comply with a good system.
- The final part consists of the inspectors' conclusions, including the corrective actions required and recommendations on how to improve if appropriate.

For some types of inspections, such as supplier audits, a much simpler style with a list of issues and required actions might be more appropriate. For regulatory inspections, there will tend to be a 'house style' used by the whole inspectorate, to ensure consistency and to prevent confusion for companies when their inspector changes.

11.5 GMP certification in the developing world

Whilst compliance to international standards of GMP is relatively well established in the developed world, there are many companies in Eastern Europe, the Middle East and Africa who are going through rapid change in order to catch up. In many cases, they are working with independent consultants, either funded privately or, more often, through EU-funded and other similar programmes. In all cases, one of the first questions that is asked of the consultant is 'How can we get our factory certified to GMP?'. This is usually because they want to develop their export market or apply for international tenders.

The answer is not a straightforward one. The easiest solution is for the national regulatory authority inspectors to carry out inspections. However, in many countries, the infrastructure is only just being developed and there is not a competent inspectorate in place. This immediately precludes the country from registering for the WHO certification scheme.

To arrange for an inspector from an EU Member State or from the FDA to visit the factory, it is necessary for a registration dossier to have been submitted. In many cases, it is far too early for the companies to think about this.

Hence, there is an impasse developing, which can apparently only be solved by encouraging the companies to work towards GMP standards in parallel with the development of the national inspectorate. Since everyone is learning together, this can lead to an interesting culture of co-operation in areas where traditionally the divide between the regulatory authorities and industry has been much wider.

11.6 Case studies

11.6.1 Case study 1

A company in the Middle East employed a GMP consultant to help it improve its level of GMP compliance as an initial step towards exporting its products to Europe. During the initial GMP inspection, it was identified that the company did not have a self-inspection programme in place. One of the recommendations was hence that such a programme should be set up.

During the second visit to the company, the consultant was told by the QA department that everything was going very well, and that many of the recommendations were already being implemented. The self-inspection programme had been planned and the first round of inspections was in progress. However, the story from the production department was a little different. They were unhappy that the QA personnel had set up 'yet another policing mechanism' and saw the whole thing as a bad idea.

On reviewing the situation with both parties, it was discovered that the QA manager had taken all the decision and had presented the production manager with a *fait accompli.* Once the objectives of the programme were fully reviewed, and the production department became involved in both the planning and the operation of the programme, they realized that the programme was about improvement rather than blame, and became much more enthusiastic about it.

11.6.2 Case study 2

In the late 1970s, the UK pharmaceutical industry was becoming used to the idea that increased legislation, GMP guidelines and a regular programme of inspections by regulatory authorities were the facts of life from now on.

A small research-based company in the Midlands had been developing a small-scale manufacturing operation in their facility, which was primarily a laboratory and office building. They were told by the DHSS inspectors (forerunners of the MCA) that they must build a purpose-built factory or cease production. They rented an old warehouse, refurbished it and moved the production equipment in. Slowly but surely, they were getting everything in place, but obviously, it would take time to reach full compliance.

A couple of months later, the first inspection of the facility was held. The managing director (MD) wanted to ensure that everything went smoothly and decided to accompany the inspector himself. He did most of the talking during the visit and insisted on answering all the inspector's questions.

Anxious to put on a good performance but blissfully unaware of the full technical requirements of GMP, the MD proceeded to give all the answers that he felt the inspector wanted to hear: of course they had a suitable ventilation system; obviously all the procedures were correctly written and in place; certainly all the personnel were fully trained. The technical manager, who was a fairly recent graduate, listened to this discussion with a sinking heart. He know that sooner or later the inspector would ask for evidence of all these assertions, none of which was accurate – and also knew that he would not be able to produce the evidence. This would reinforce the view of the inspector that

the company was badly run and technically incompetent, rather than a small company trying to deal as best it could with a rapidly changing environment.

Whilst this case study is more than 20 years old, the same story is being repeated today in countries that are behind the developed world, and are desperately running to try to catch up.

11.6.3 Case study 3

A major multinational pharmaceutical company with subsidiaries around the world had a programme of inspections that were carried out in all their factories. The inspectors were drawn from corporate headquarters and had expertise in production, QA, development and engineering. On average, the inspections took place on an annual basis.

When the inspections were first started in the mid-1980s, the role taken by the inspectors was primarily a policing one. It was an opportunity to check up on what the subsidiaries were doing and to make sure that the quality of the product was consistent all around the world. The response from the subsidiaries was mixed, but in many cases, there was a feeling that 'those guys from head office turn up, criticize all the hard work that we have done under difficult circumstances, and then go home, leaving us with a long list of things that we have to do – and pay for!'.

In the early 1990s, the pharmaceutical world was starting to change and a much more commercially aware approach was required. The inspectors found that they had to justify their expensive trips in financial terms. It was no longer good enough to say that quality demanded these inspections. After all, each of the subsidiaries had their own QA systems, QC controls and national regulatory bodies to satisfy.

The emphasis of the inspections changed and the inspectors began to take the role of coaches, helping the subsidiaries to improve not only their quality standards, but also the business performance of the factory. Benchmarking exercises were used to disseminate best practice from individual factories to the rest of the group. The entire process became much more positive and the annual visits became a welcome part of the calendar for all the subsidiaries.

12

Pharmaceutical microbiology

12.1 Introduction

This chapter covers a variety of topics, which are all connected by their microbiological associations. We begin with an overview of basic microbiology, as it relates to the pharmaceutical industry. Next there is a discussion of the microbiological aspects of raw materials. (In the pharmaceutical industry, water is a key raw material, as well as being a major element in the provision of services and cleaning; for this reason, it is dealt with on its own in Chapter 13.) There is a short section on the microbiology of non-sterile products, but the remainder of the chapter then moves on to the main topic of sterile manufacturing.

We start with a review of the main types of sterile products and other items that are sold in the sterile state. Next there is a discussion of the manufacturing of sterile products, with particular emphasis on the differences between terminally sterilized products and those that must be manufactured aseptically. There follow sections on the contamination risks inherent in a pharmaceutical factory and the various methods used within the industry to control contamination levels; and also the different monitoring programmes that are needed to ensure that contamination has been controlled. Finally, the huge topic of sterilization is reviewed briefly.

12.2 Overview of micro-organisms

Micro-organisms are covered by three of the five defined life forms: fungi, protista (photosynthetic microbes) and prokaryotes (bacteria). In the context of pharmaceutical manufacturing, the main attention is generally paid to bacteria and this will be reflected in this section.

Bacteria

Bacteria range in size from 0.2 to 10 µm and most are <5 µm in length; an exception to this are the spiral organisms, which can grow to 100 µm long. They are found in three basic shapes: round, rod-shaped or spiral. The first two are the most commonly found in our environment.

Round bacteria are called cocci; common examples of the cocci genus are *Staphylococcus* and *Streptococcus,* both of which are associated with infections. Rod-shaped bacteria are called baccilli; common examples are *Escherichia coli*, which is associated with intestinal disorders, and *Pseudamonas* genus, which is associated with infections.

Whilst most living organisms require oxygen to survive, this is not true of all bacteria. Some bacteria exist as aerobes, which means that they do indeed require oxygen to live. Alternatively, there are other bacteria that are called anaerobes, since they are killed by the presence of oxygen. There are also two intermediate types: aerotolerant anaerobes, which can exist with or without oxygen; and facultative anaerobes, which can grow with or without oxygen, but develop better in the presence of oxygen.

Bacteria can be divided into pathogenic organisms, the ones that cause disease, and the non-pathogenic organisms, which are present in the environment all the time and, in many cases, are necessary for healthy living. All the examples given above are pathogens. However, in fact, the vast majority of bacteria are non-pathogenic. In pharmaceutical terms, it is more important to prevent contamination with pathogens. That is why the pharmacopoeial monographs for water quote a maximum level for total bacterial count (which is about particulate reduction as much as anything), but specify the absence of pathogens such as coliforms or pseudamonads.

Bacteria can exist in one of two states. Under optimal conditions, the organism is in the vegetative state and continues to feed and grow. Under these conditions, cells are relatively easy to destroy, and will tend to be controlled by disinfection and sanitization processes. Cocci only ever exist in this state and hence are relatively easy to kill. However, they are quite resistant to drying, and hence can exist on skin or dry surfaces or in air over time.

Under adverse conditions, some bacteria, such as *Bacillus* species can form spores. These are similar to seeds in that they produce a protective casing and remain dormant until more favourable environmental conditions exist. This will often occur when there is insufficient moisture in the environment. For bacterial spores to be killed, full sterilization conditions need to be achieved.

Fungi

Fungi are more susceptible and will tend to be controlled by the measures that are in place to control bacteria. There is not generally much emphasis on fungi in the context of pharmaceutical microbiology. However, it is fungi that cause spoilage of raw materials and/or packaging materials under damp conditions and this is one of the reasons why it is important to check the condition of all deliveries that are received in the factory.

Endotoxins

The other area of importance in relation to pharmaceutical manufacturing is that of endotoxins, also called pyrogens. Endotoxins are toxic substances, consisting of lipopolysaccharide and lipoprotein complexes that are bound to the cell walls of Gram-

negative bacteria such as *E. coli* and *Pseudomonas* species. When the bacteria rupture or disintegrate, endotoxins are released. When endotoxins enter the bloodstream, they can trigger an immune reaction.

Whilst endotoxins are rarely fatal, they can cause fevers. For all products that are to be administered parenterally, there is a requirement not only for sterility but also for an absence of pyrogens.

12.3 The microbiology of raw materials

One of the tests that are carried out on many raw materials before they are approved for use is an analysis of microbiological content. The specification for the material should contain not only chemical and physical data, but also the maximum permitted level of microbial contamination. What that level should be set at will depend on a number of factors including the following.

- The source of the material: a raw material produced from natural sources such as plant matter will tend to have a higher microbial content than a material produced synthetically.
- The intended use of the material: a raw material that is going to be used in the manufacture of a clean liquid or an ointment without preservative will tend to have a tighter microbial limit than one being used in the manufacture of tablets.

If a raw material is to be used in the aseptic manufacture of a sterile product, it will usually have been purchased ready sterilized from the supplier. In this case, it is acceptable to delay the sampling and testing of the container until it has been transferred into the sterile area and manufacturing is due to commence. This is because the normal conditions under which samples are taken, whilst suitable for non-sterile materials, would not provide sufficient protection for a sterile material.

12.4 Non-sterile products

Non-sterile products are those which, whilst being pharmaceutically clean, do not need to be sterile when they are administered to the patient. They include dry products, such as tablets or capsules, oral liquids (solutions and suspensions), suppositories, and some ointments and creams. Even though there is no requirement for sterility, it is important to ensure that the product is not heavily contaminated and hence a number of precautions need to be taken.

Non-sterile products are generally produced in ‘clean’ conditions. Although there are no stated rules, it is the custom and practice within much of the industry that, wherever a raw material, intermediate or finished product is exposed to the atmosphere, an area classification of at least ISO grade 8 is required.

The conditions under which manufacture is carried out will increase in stringency if the nature of the product is such that microbial contamination is likely to occur. For example, dry products tend not to support microbial growth. On the other hand, a cream or an ointment, which is water based, may be susceptible to contamination, depending on whether the formulation contains a preservative or not.

On occasion, manufacturing requirements may be driven by national regulations. For example, in Russia, the microbial limit for oral suspensions that are to be given to infants of less than 12 months is 50 cfu/ml, whereas for children of more than 12 months, it is 500 cfu/ml. Hence in a multipurpose facility, the higher limit would be the design parameter to be achieved.

The topic of environmental monitoring is covered in detail later in this chapter. In the context of non-sterile manufacturing, it is sufficient to say that monitoring programmes should be designed to suit the design of the facility and the process, the required results and the historical profile as obtained during validation.

12.5 Sterile products

Sterile products are those products that need to be free of micro-organisms (and particulates), owing to the method in which they are administered to the patient. The largest class of sterile products is the small volume parenterals (SVPs), which are the injectable products. Other types of sterile products include large volume parenterals (LVPs), some ointments and creams, and eye drops. Additionally, there is a wide range of medical devices that need to be sterile when sold.

12.5.1 Small volume parenterals

Primary containers in the case of SVPs are ampoules, vials or pre-filled syringes. They may be made of glass or plastic. The fill-volume in an SVP is generally 10 ml or less. In most cases, it is 1 or 2 ml.

Ampoules contain single unit doses. They are more common in Europe than in the USA, where there is concern about the particulate contamination caused by broken glass at the point of opening. They are the cheapest to manufacture and purchase. The product within an ampoule will generally be in liquid form.

Vials can either be single unit or multiunit doses. They have a rubber disc within the seal, which can be pierced a number of times as the doses are taken out. Product within a vial may be liquid, powder or a freeze-dried pellet. In the latter two cases, the drug is dissolved or reconstituted with a suitable diluent prior to administration of the injection.

Pre-filled syringes are single-unit dosage forms. They are the most convenient to use, since the needle is attached within the pack. They are the most expensive to manufacture and purchase. The product in a pre-filled syringe will always be liquid.

12.5.2 Large volume parenterals

Primary containers for LVPs are bottles or bags. The former may be made from glass or plastic; the latter tend to be made from plastic. The fill-volume can be anything from 25 ml to 1 litre. LVPs are the products that are associated with administration of drips (blood products, saline) or transfusions.

12.5.3 Ointments and creams

Sterile ointments and creams are normally filled into tubes. These tubes can be made of metal, but are more usually made of plastic. The fill-volume is usually 5 ml or less because, once the tube is opened, the sterility can no longer be guaranteed.

In some cases, ointments and creams are packed in more novel containers, such as the pump dispenser, which allows a measured amount to be dispensed without the risk of the remainder of the product becoming contaminated.

12.5.4 Eye-drops

Sterile eye-drops are liquids, which are filled into dispensing containers such as dropper bottles. The fill-volume is generally less than 10 ml.

12.5.5 Medical devices

The range of sterile medical devices is very large. They come in all shapes and sizes, from single injection needles, through to multicomponent dialysis kits.

12.6 Sterile manufacturing

The manufacturing of sterile products takes place in a number of stages, and the exact sequence depends on a number of variables, including the nature of the product and the type and material of the primary container. In general terms, the sequence of events will be as follows:

- the preparation stage for the bulk batch of drug, the primary packaging components and ancillary items, such as filling machine parts;
- the filling and sealing stage;
- the inspection stage; and
- the final packaging stage.

In addition, there will be the sterilization stage, which will vary in position, as discussed below. For some dosage forms, there will also be a leak-test stage after filling and sealing.

The type of manufacturing that is appropriate will also have implications for the classification of the manufacturing areas.

12.6.1 Area classifications

Over recent years, there have been a variety of standards that have been used across the world for defining the classification of air to be supplied to different types of manufacturing area. A number of these are listed below and referenced in full in the Bibliography:

- US Federal Standard 209D: with the familiar classes of 100, 10 000 and 100 000, this is the terminology that was most commonly used in many countries; it was updated in the 1990s to 209E, with a change to SI measurements, but the new terminology did not generally move into common usage.
- BS 5295: this is the UK standard that was issued in 1989, with classifications running from E to K; it tended to be used within UK only.
- EU guidelines, Annex 1: with classifications running from A to D, this is the terminology that is common in many countries, not just in Europe.
- Parenteral Society Technical Practice Monograph No 2: an industry-specific guideline on environmental contamination control with particular reference to microbial contamination.
- FDA guidelines on Sterile Drug Products: issued in 1987 and relating to aseptic manufacturing processes.

Although the industry-specific standards are written in relation to the manufacture of sterile products, custom and practice within the industry is leading to appropriate levels of classification being used for non-sterile manufacturing as well.

From 1992 onwards, the authorities and industries in Europe, USA and the Far East have been working with the Committee for European Normalization (CEN) and the International Standards Organization (ISO) to produce a worldwide standard for airborne cleanliness. The first part of the standard was published in May 1999 as: EN/ISO 14644 Clean Rooms and Associated Controlled Environments, Part 1, Classification.

There are a further seven parts of the standard either published or in preparatory stages. These are listed in the Bibliography. The standard has been adopted within the EU and it is expected to replace the existing standards in the USA, Japan and Korea in the near future.

Table 12.1 Comparison of terminology used in the main standards

Approximate particles per m^2 >0.5µ	US 209D	EU GMP	BS52995 1989	ISO EN 14644-1 1999
3530	100	A or B	E or F	5
35 300	1000		G or H	6
353 000	10 000	C	J	7
3 530 000	100 000	D	K	8

The new standard uses classifications from 5 to 8. Table 12.1 shows the comparison of the different terminology from the main standards used within the industry.

For the remainder of this chapter, the ISO terminology will be used for consistency.

12.6.2 Terminally sterilized products

Terminally sterilized products are the ones that can be sterilized after filling, in their sealed containers. Since the product at this point is fully contained and will not become

exposed to the atmosphere until it is administered to the patient, this is the preferred method for manufacture.

For terminally sterilized products, the sequence of events is preparation, filling and sealing, sterilization, inspection and final packaging.

Products that come under this category include: ampoules and vials containing liquids, which are thermostable and can be sterilized by moist heat; ointments and creams that can be sterilized by irradiation; and medical devices that can be sterilized by irradiation or gases.

Where products are going to be sterilized after filling, it is not necessary to manufacture them under aseptic conditions. The main concern is to minimize the bioburden within the dose unit during the preparation and filling stages, so that a greater level of bacterial kill can be obtained during the sterilization phase. (For a full discussion on sterilization, see later in the chapter.)

It is normally acceptable for preparation of bulk drug and components to take place in a grade 8 environment. However, there are situations in which the product is considered to be 'at risk', in which case, it would be necessary to manufacture the bulk in a grade 7 environment. Such a situation would arise if the product is susceptible to microbial contamination, or if it is likely to be held in the bulk or filled state for a period of time before it can be sterilized, or if the processing takes place in open vessels.

For filling of these products, it is normally acceptable to use a grade 7 environment. However, once again, there are situations in which the product could be considered to be 'at risk'. In these cases, filling should take place in a grade 5 environment, with a grade 7 background. Conditions that constitute a risk include primary containers with wide necks or filling operations that necessitate the unit being exposed to the atmosphere for a period of time between filling and sealing.

12.6.3 Aseptic manufacture

Where it is not possible to sterilize the product after filling, it must be manufactured under aseptic conditions. This means that all materials and components are sterile at the point that the product is filled and sealed into the primary container.

For aseptic products, the sequence of events is thus preparation, sterilization, filling and sealing, inspection and final packaging.

For bulk product, the method of sterilization will differ, depending on the nature of the drug and its physical form. Liquids may be filtered into the filling room after manufacturing. Powders will tend to be irradiated, double-wrapped and passed into the filling room via a hatchway, with the outer wrapping being removed at this point.

For components, the method will vary with the material. For glass, the normal method would be dry heat; for plastic components, irradiation or gassing is used; for rubber and metal stoppers, a mixture of methods is used, varying from heat and chemical methods to irradiation.

The classification of the facilities for aseptic manufacturing varies with the activities that take place in them. Glass vials and other components that are washed and then sterilized into the filling suite should be prepared in a grade 8 area. Solutions or other bulk product that can be filtered into the filling room can be manufactured in a grade 7 area. However, if no filtration is possible (e.g. with biological suspensions), a grade 5 area with a laminar flow, with a grade 5 background is necessary.

All other activities associated with aseptic manufacturing must be carried out in a grade 5 area with a laminar flow, with a grade 5 background.

12.6.4 Mixed manufacturing

The requirements for area classifications described above should be considered as the minimum acceptable standard. Many companies have a portfolio that contains a mixture of products for which terminal sterilization is an option and others for which aseptic manufacture is mandatory. In these circumstances, it is preferable to have separate facilities for the different types of product, since the controls and requirements for aseptic manufacturing are far more stringent than those required for terminal sterilization.

However, it is not compulsory to have such an arrangement. It is perfectly acceptable to produce the two types of product within the same facility, providing that all products are manufactured to the same (higher) level. Once the facility has been validated as acceptable for the manufacture of aseptic products, all products should be produced as such, even if some of them will be terminally sterilized after filling. To attempt to operate under two different standards within the same facility, depending on which part of the product range is currently being produced, would be an impossible task.

12.7 Risks of contamination and their control

There are a number of possible sources of microbiological contamination within the manufacturing environment. Each requires specific measures to minimize or eliminate the risk. The controls can be associated with a number of different aspects of manufacturing: personnel working in the clean rooms; the design and construction of the facility; the design and construction of the equipment; the way that the facility is operated; and the programmes for cleaning and sanitation.

12.7.1 Personnel

The greatest source of contamination within a clean or sterile area comes from the personnel working in there. During sterile manufacturing, it is important that the number of people working in the area is kept to a minimum, particularly in an aseptic operation. Where possible, in-process controls are performed outside the clean room. Alternatively, operators may be trained to carry out tests themselves, to reduce the number of indirect personnel who enter the area.

There should be a regular training programme for all personnel who routinely enter the sterile areas – both direct operators and service personnel, such as cleaners and mechanics. This training should not only cover the job itself, but also hygiene and the basics of microbiology.

To avoid cross-contamination, it is important that personnel who have worked with animal-tissue material or live micro-organisms do not enter the sterile area. If this cannot be avoided, then strict decontamination procedures must be followed in all cases.

High standards of personal hygiene are important for all aspects of pharmaceutical manufacturing. It is even more important in the case of sterile manufacture. Periodic health checks and monitoring by swabs are important in the identification of conditions that can cause contamination. In addition, operators should be trained to report such conditions themselves.

With regard to clothing, there are some rules that are the same in all factories. There should be no outside clothing brought into the area, and watches and jewellery should not be worn (nor should cosmetics, since these may shed particles). Some companies insist on the removal even of wedding rings. There should be a written procedure for changing and washing.

However, when it comes to the detail of that procedure, there are a variety of approaches that may be taken. In particular, the order in which different pieces of clothing are taken off or put on, and the point at which hands are washed will vary between companies. There is no one right answer to this question and the important point is the logic of the approach and the consistency with which it is applied.

In the grade 8 area, a simple coat, hat and shoe cover is sufficient; in the grade 7 area, a one- or two-piece trouser suit is preferable. Hair, including facial hair, must be covered. In grade 5 areas, masks and gloves are added to the outfit.

Arrangements must be in place for the laundering and sterilization of clean-room clothing. This should be carried out in a controlled environment. The use of contract laundries for this requires an audit by the company to ensure that appropriate procedures are in place.

It is important to remember that there may be visitors to the sterile area (although these should be kept to an absolute minimum). An appropriate procedure for clothing and supervising visitors should be in place. Visitors may need special training before entry to the sterile area is permitted. This special training is necessary to ensure that they can conform to entry procedures.

12.7.2 Premises

There are a number of specific aspects to the design and construction of premises that are used for the manufacture of sterile products, which are designed to reduce the risk of both microbial and particulate contamination. Entry to all processing areas is through airlocks. For personnel, these airlocks generally take the form of changing rooms that have a variable number of interconnecting rooms, depending on the classification of the area. Separate airlocks should be provided for the entry of materials into the area. The doors at either end of an airlock should be interlocked so that they cannot both be opened at the same time. (Although, in some countries, this is not permitted by the fire authorities and alternative solutions may be required, such as visual or audible alarms.)

Processing takes place in suites of rooms, with different classifications depending on the activities carried on in them. The classifications relate primarily to the supply of air to the rooms as discussed previously. The rooms are designed to reduce the accumulation of dust, which could be a source of microbial and/or particulate contamination, with all exposed surfaces being smooth and unbroken. Ideally there will

be false ceilings, which are sealed so that nothing can fall from the void above. This also permits access to light fittings from above, allowing maintenance without stopping production. Wherever possible, pipes and ductwork should be outside the area or boxed in. Sinks and drains should be avoided, if possible, and must not be installed in aseptic areas. Drains should have cleanable traps and air breaks to prevent back flow. Floor channels must be open and easy to clean.

12.7.3 Equipment

Design

Equipment for use in the sterile area should be designed so that it achieves two specific objectives:

- It can be operated with the minimum of personnel interference, thus reducing the possibility of contaminating the product.
- It can be easily sterilized by moist or dry heat sterilization. It should be easy to install change parts for different pack sizes.

Sterilizers should be designed with a door at each end (known as double-door autoclaves or double-ended autoclaves) to eliminate the possibility of mixing up sterile and non-sterile materials. This is particularly important for sterilizing components that are going into the filling room. They are loaded in the preparation area and unloaded in the sterile area, although preferably in a buffer room rather than directly in the filling room.

It is important that the zone in which the product is to be exposed is protected to the maximum extent possible. This requires the installation of laminar flow cabinets over the piece of equipment, to provide a grade 5 environment and to ensure a supply of filtered air flowing with positive pressure towards the surrounding areas.

It is also necessary to ensure that the locations of the equipment and the operator do not cause a risk to the product by interrupting the flow of filtered air. There should be a warning system to indicate a failure in air supply, such as a manometer, measuring pressure differentials or an audible alarm.

Maintenance

Where possible, maintenance of equipment should take place outside the area. However, if this is impossible, it should be done when there is no work going on and should be followed by a complete clean-down and disinfection. Tools for such work should be sterilized before being taken into the area. It is even better if a full set of sterilized tools can be stored in the area specifically for this purpose. After maintenance has been completed, there should be a documented procedure for obtaining approval to resume operations in the area.

It is permissible to have transport systems to take product from the filling room to the sterilization/finishing area, but there must be a dead-plate across the actual interface between the two areas. There should be no conveyor belt passing between two areas of differing classification, unless that belt is continuously sterilized, for example, in a sterilizing tunnel.

New technology

There is a growing use of isolator technology within pharmaceutical manufacturing as a means of reducing the potential for microbial contamination within an aseptic processing area. Whilst there are many different designs, the basic concept is to minimize the amount of human intervention in the process by use of some type of 'glove box' arrangement. Apart from reducing the possibility of microbial contamination, it can be a lower cost option, since the background environment can be as low as grade 8.

The points of transfer of material into and out of the isolator are the key risk areas and must be carefully controlled. Validation of an isolator must also pay close attention to the quality of air achieved and the airflow patterns, the procedure for sanitization, and the problems associated with rupture or leakage.

One specialized piece of equipment that is used in some manufacturing areas is the blow/fill/seal technology that is used to form plastic containers from thermoplastic granulate, to fill them and seal them in an in-line continuous process. Such technology can be used for the manufacture of aseptic products or terminally sterilized products. In both cases, a grade 5 laminar flow air shower is required, with a grade 7 background in the former case or a grade 8 background in the latter case.

Key issues to be considered in using such technology include the design of the equipment, the clean-in-place (CIP) and steam-in-place (SIP) systems, and any manual operations that need to be carried out prior to filling.

12.7.4 Operation of the facility

At all times, there should be measures to ensure that contamination is minimized. The processing of preparations containing live micro-organisms is not allowed in the same facility as other pharmaceuticals. Inactivated products can be processed in the same facility providing validated procedures are used.

During processing in sterile areas, it is important that the amount of activity is kept to a minimum. As discussed above, the greatest source of contamination in a sterile area is the personnel. Hence, the more automatic the process and the fewer people in the area the better. These areas should be built with plenty of windows to increase the visibility and remove the need for extra people to go into the room during processing.

No unsuitable materials should be used in the areas. All furniture and fittings should be of metal or plastic rather than wood. Paper may need to be used in the area, for example, for batch documentation, but this should be kept to a minimum. Bonded paper or lint-free paper is available. Paper should not be used in a class A area at all. Alternatives include plastic sheets and permanent markers. It goes without saying that extras such as calendars and notices should be excluded.

The microbiological contamination load or bioburden for both raw materials and for products prior to sterilization should be kept to a minimum. There should be documented limits in all cases.

Extreme care must be taken with materials that have been sterilized into the area for use in aseptic production, such as primary containers and filling machine parts. After removal from the sterilizer, they are stored under a laminar flow cabinet until used. All packs must be marked with the date of sterilization and there must be a procedure stating how long an item can remain in the area before it needs to be resterilized. There

must also be a validated maximum storage period that is allowed between manufacture of bulk product and filling into primary containers. This will depend on the nature of the product and whether it has been sterilized into the area or is going to be terminally sterilized.

12.7.5 Cleaning and sanitation

Clean and sterile areas must have a documented and planned programme of sanitation. Procedures must include details of who is responsible and the frequency of cleaning in each area; this will vary for different rooms, depending on the activities and the risk to the product. There should also be details of the methodology, including preparation of cleaning materials.

All cleaning materials should be evaluated and approved by QC. For disinfection, there should be rotation between different chemicals, in order to prevent microbial resistance building up. Dilutions should be prepared with purified water and should only be stored for a short period of time, as specified by QC or the manufacturer. The use of freshly prepared dilutions is by far the best approach. They should be sterilized before use in the sterile area.

The fumigation of the area, for example, with formaldehyde, in order to decontaminate it used to be a very common practice, but is used less these days. It is an effective method, but requires careful use and adequate 'degassing' afterwards. With effective ventilation systems, it should be possible to eliminate the need to carry out this process or at least to reduce its frequency.

12.8 Validation and environmental monitoring

In a factory that is producing sterile products, the level of QC requirements is higher then in any other. In particular, there is a very high level of environmental monitoring required. This monitoring covers not only microbiological contamination, but particulates as well. However, since this chapter is dealing with microbiological aspects only, the latter topic will be omitted.

12.8.1 Monitoring of the air

The first aspect of microbiological monitoring of the environment relates to the air supplied to the rooms. This is carried out in two ways: firstly, by monitoring the operation of the ventilation system (the inputs); and, secondly, by checking the quality of the resulting air (the outputs).

The number of air changes within a room is calculated from the air volumes supplied to the room. This will be carried out at validation and regularly thereafter.

The HEPA filter integrity is tested by a number of means. An aerosol generator can be used to send an aerosol across the filter and a photometer used to view the amount of aerosol that passes downstream. This will show if there is any damage to the filter. Additionally, a manometer can be used to measure the pressure differential across the

filter. These tests will be carried out when filters are installed and should be repeated at least annually.

A number of the environmental parameters can be monitored automatically and new factories often have sophisticated building management systems that not only monitor, but also make adjustments if required. However, if a factory does have such a system, it is important to ensure that personnel looking after the system fully understand it. From experience, it can be all too easy to assume that everything is under control and not notice when something goes wrong. An important element of the original validation work is to ensure that all the controls are working as intended.

In terms of measuring the outputs, there are a number of methods for taking samples, but the simplest and most widely used is to place open settle plates of growth medium on the floor for around four hours. (The exact time period has to be developed to suit local conditions.) The number of plates required depends on the classification and use of the room, and can be determined from international standards, such as ISO 14644 Part 1. The location of the plates will have been determined during validation and will be based on the risk to the product and the level of activity in the area. It is not necessary to obtain zero-growth results from these plates, but a validated pattern of likely contamination will be established and significant deviations need to be investigated. If zero growth is observed, then low levels of bacteria are inoculated on to the plate to demonstrate that it will support growth.

12.8.2 Monitoring of surfaces

Monitoring of surfaces is generally carried out using swabs. Emphasis should be placed on the areas that come into contact with the product and in these areas, zero-growth results are expected. This method of monitoring, carried out before and after cleaning and disinfection, can be used to validate the methods of sanitation being used.

12.8.3 Monitoring of personnel

Finally, it is necessary to monitor the micro-organisms arising from the personnel in the clean rooms, since these are the greatest source of contamination. Samples are generally taken by swabs from clothing and by ‘finger-dabs’ on to plates. Sampling must be representative of the situation during operations, hence if the operator normally wears gloves and disinfects them before use, the samples should be taken after that process has been carried out.

12.8.4 Media trials

A media trial is an important part of validating an aseptic filling process. It involves filling a growth medium into primary containers and incubating them to see if any are contaminated. There are a number of factors to be taken into account when reviewing a media trial programme.

Firstly, it is important that the trial accurately reflects the true situation during filling. Operators normally working in the area, in the same way that they always do, should carry out the media trial. Secondly, the medium used must be capable of supporting growth of a wide range of micro-organisms, including those likely to be found in the filling room. Negative controls must be carried out to prove that the medium is sterile before use and positive controls to prove that it will support growth. Thirdly, it is important that sufficient units are filled to ensure that low levels of contamination will be picked up. This should be at least 3000 units. However, for trials involving small batch operations (where a small batch is defined as one of less than 3000 units), the trial size should be at least as large as a normal batch. If there is usually a pause for a break during normal operations, this should be simulated.

Obviously, the objective is for zero growth in the containers. However, a pass level of less that 0.1 per cent contamination with a 95 per cent confidence level is considered acceptable. Any contaminants should be isolated and identified.

The media trial should be repeated at regular intervals; between quarterly and six-monthly is likely to be the standard. However, it is important to ensure that full cleaning, to remove all growth medium from the area, is carried out before filling starts again.

The above is only a brief overview of the topic of media trials. A full discussion is presented in the PIC/S document *Validation of Aseptic Processes*.

12.9 Sterilization

This section deals with sterilization, with particular reference to sterilization of products, although other items are referred to as well. There are a number of available methods, each of which has advantages and disadvantages. In each situation, consideration needs to be given to which is the most appropriate to use. However, in general terms, heat sterilization should always be the preferred method, if it can be used.

In the process of product development there is a document that has been issued by the EU, which provides a useful decision tree for choice of method of sterilization. This document (CPMP/QWP/054/98) has also been adopted by a number of other countries; for example, it was adopted by the Therapeutic Goods Administration (TGA) in Australia.

12.9.1 Sterilization by heat

Heat sterilization is usually carried out in one of two ways. Moist heat sterilization uses an autoclave and either a porous load or fluid load cycle, depending on the type of material being sterilized. Both types of cycle can be carried out in the same autoclave. For dry heat sterilization, either an oven or a sterilizing tunnel is used.

Moist heat sterilization

Moist heat sterilization is a combination of temperature, time and pressure. Hence, all parameters must be recorded and shown to achieve minimum conditions. Porous load cycles are used for sterilizing components, such as stoppers for vials, clean area

clothing, or machine parts and other ancillary items. Removal of all air from the chamber and replacement with steam is a key characteristic of this type of cycle. In the case of components, they must be wrapped in material that allows removal of air and entry of steam, but does not allow recontamination afterwards. It is important that all parts of the load are in contact with water or water vapour throughout the cycle. The quality of the steam is also critical; the use of a clean steam generator is recommended.

Fluid load cycles are used for the sterilization of filled containers of product. They are based on saturated steam, which is used for glass containers, such as ampoules or vials; steam and air, which is used for LVP bags or blow fill seal containers; or hot water, which is used when the product or container will not stand exposure to steam. Although it is important to ensure that there are no pockets of air left in the chamber, the complete removal of air is less important.

Dry heat sterilization

Dry heat sterilization is the method that is used to remove pyrogens as well as micro-organisms. It takes place in an oven or sterilizing tunnel and is a combination of temperature and time only. However, the temperature is much higher than for moist heat. This method can be used for dry components, such as empty ampoules and vials. There should be air circulation within the chamber and a positive pressure to prevent ingress of non-sterile air. The air should be circulated through high-efficiency particulate air (HEPA) filters.

12.9.2 Irradiation

There are a number of different types of irradiation: gamma, electron beam, alpha, beta and pulsed light.

This method of sterilization generally takes place in a stand-alone, dedicated facility. It is very rare for a pharmaceutical company to have its own irradiation plant. A company that did have such a facility would be unlikely to have sufficient demand to keep it operating full time and hence would be able to offer a contract sterilization service to other companies in the region or the country.

Radiation sterilization is used primarily for heat-sensitive materials and products, such as ointments and for plastic components prior to filling. However, care must be taken to ensure that the materials are compatible and not radiation sensitive. This would form part of the original validation work.

In many countries, ultraviolet radiation is used as a ‘sterilizer’. This should be treated with care. Ultraviolet irradiation is not a very effective method of sterilization, although it can be useful in maintaining a low level of micro-organisms once obtained, for example, in purified water systems. Its use requires careful validation.

As with heat sterilization, it is important to monitor the effectiveness of the sterilization cycle. In the case of radiation, dosimeters are used that provide a quantitative measure of the dose received. These are inserted within the load in sufficient number to ensure that there is always one in the chamber. Radiation-sensitive discs on the outside of packs are used to prove that the load has passed through the chamber. Like autoclave tape, they do not prove sterility.

12.9.3 Ethylene oxide sterilization

Ethylene oxide gas (ETO) is only to be used as a sterilant if no other method is available. The gas is explosive in air at relatively low concentrations and leaves behind significant residues in the product that need to be removed before the batch can be inspected, packaged and released for sale on to the marketplace. This method is used for plastic items, such as medical devices that are both heat and radiation sensitive. The cycle is a combination of time, temperature, humidity and gas concentration. The first three parameters are generally recorded directly, whilst the last is recorded indirectly. The usage of gas is also calculated by weighing the cylinders before and after the cycle to cross-check that the gas usage is as expected.

It is important that direct contact between the gas and any micro-organisms on the product takes place. Additionally, it is necessary for any micro-organisms to be in a moist environment, since the rate of kill is inversely proportional to the dryness of the surroundings. Hence the packaging must be suitable to allow in moisture and gas.

ETO sterilization uses biological indicators to measure the effectiveness of the cycle routinely. Their use should be controlled and positive controls employed to ensure that they are still viable.

As mentioned earlier, one of the problems with ETO is that residues are left behind at the end of the cycle. The processing cycle must include a validated degassing period, where the load must be stored in a suitably ventilated room under quarantine.

12.9.4 Filtration

It has already been discussed above that terminal sterilization is the preferred method for product as it reduces the risk of recontamination. However, this is not possible for some materials, such as vaccines and insulin. In this case, sterilization by filtration into a sterilized container is required. The filter should have a nominal pore size of no more than 0.22 µm. However, it should be remembered that viruses and mycoplasmas might not be removed by this method.

In order to reduce the risks associated with the filtration method, double filtration is recommended. There is usually a pre-filter before the main one anyway, but in addition, a final filter, just prior to filling, should also be used if possible. Where double filtration is not practised, then further monitoring is required. Media fill validation trials and pre-sterilization bioburden counts are two possible methods. (See Section 12.8.4 for more details of media fills.)

Filters should be integrity tested after use and in some cases are also tested before use. This requires the use of equipment such as a bubble-point tester. In addition, validation of the method will have produced standard times and pressure differentials for a given volume of liquid. Any variations from this should be noted and investigated.

Filters should not be used for more than one working day, unless longer use has been validated. Reusable filters are permissible, but there must be validated methods of cleaning, resterilization and storage.

12.9.5 Validation and monitoring of sterilization cycles

Validation of the method of sterilization is essential, particularly as sterility testing is always a destructive test and can only be carried out on a sample of the batch. A regulatory inspector would be particularly interested in validation results for any methods that are not in accordance with national standards, or for materials that are not solutions. It is also important that the method of sterilization being used is the one that was originally validated for the process or product.

Biological indicators can be considered as part of the monitoring of the sterilization process. Their use should always be controlled to prevent contamination of the facility and product with live micro-organisms.

It is very important that a company has effective methods for separation of sterilized and unsterilized materials. Ideally, sterilizers should be double-ended, so that there is no cross-flow of materials with the consequent risk of mixing. Containers must be clearly labelled and indicators, such as autoclave tape or irradiation discs, are used to show that a particular load has passed through the sterilizer. However, it is important to remember that this is all the indicators prove. They are not in themselves proof of sterility.

All sterilization cycles are monitored using appropriate recording equipment. This will provide a record of all the cycle parameters. For heat sterilization, probes are located at the coolest part of the chamber so that they are recording the worst-case situation. The charts taken from these recorders will form part of the batch processing records.

For any given cycle and load within a moist or dry heat sterilizer, there will be a period when the sterilizer is heating up, before the correct temperature is reached. The recording of the cycle time should not commence until this heating period has been completed. Similarly, there will be a cooling down period at the end of the cycle. Any liquid or gas used to cool the load must be sterile so that it cannot cause recontamination.

Sterility testing

Sterility testing is required as part of the process for batch release for all sterile products unless approval has been obtained for parametric release. It is important that representative samples are taken from the batch. For aseptic production, this would be the start and finish of the batch, and after any major breaks in work. For terminally sterilized products, the coolest part of the load should be sampled. If a batch is sterilized in more than one load, then samples should be tested from each load.

As discussed previously, sterility testing will only be part of the quality assurance for the batch, and results should be considered in the context of all the other tests and monitoring carried out during production.

If a test fails, it could be a production problem or a laboratory problem. If a test is to be repeated, as allowed by the national drug regulatory authority, it should be conducted in strict conformance to the pharmacopoeial method in force. Batches that fail the initial sterility test, but pass a second one, should only be released for sale if a full evaluation of the production record and environmental monitoring proves that the original test was invalid.

13

Water for pharmaceutical uses

13.1 Introduction

In the pharmaceutical industry, water is a very important material. It is used in large quantities for cleaning and sanitation purposes. In addition, it is a major raw material, used in a variety of dosage forms including injections, creams, oral liquid products and even as a granulating solution in dry product manufacture. The preparation of water is a key technology within our factories.

There are a number of documents referenced within this chapter. However, two in particular are worthy of mention. Since late 2000, the EMEA Quality Working Party has been involved in discussions on pharmaceutical water. A draft document CPMP/QWP/158/01 has been issued and is likely to become a key guidance source for European manufacturers. In addition, there is an ISPE baseline guide on the subject of pharmaceutical water.

13.2 Types of water

There are a number of different quality grades for water, which are described below. The grades are defined in terms of the chemical, physical and microbiological characteristics of the water. The relevant standards are given in the various pharmacopoeias. Since this chapter is related to Chapter 12 on pharmaceutical microbiology, reference is only made to the microbiological aspects of each grade.

Untreated water

This is the raw water that may enter the company either from a local source, such as a private borehole or, possibly, from the metropolitan system. It provides the raw material for the water treatment plants and is also used for non-process purposes, such as fire-security systems or irrigation.

There is no microbial standard for untreated water; however, it is important that the bioburden is known, in order to ensure that appropriate pre-treatment and treatment systems are in place to provide the right quality for the higher grades of water. It is also necessary to review the standard of supply over a period of at least 12 months to ensure that there are no significant seasonal variations. For example, at times of low water levels, the microbiological contamination levels are likely to be higher than normal.

Potable water

Potable water is either delivered by the metropolitan system or obtained by the treatment of raw water. It is used primarily for drinking. It must be of a quality that is at least as good as one of the international or national standards such as EC directive 8017781EC, the USA EPA guideline, EPA140 CFR 141.14 & 21 or that published by the WHO. The microbiological standard is typically <500 cfu/ml and the complete absence of coliforms.

Process water

As with potable water, process water is either delivered by the metropolitan system or by the treatment of raw water. It is used for washing of equipment, cooling of process equipment, manufacture of active pharmaceutical ingredients and as the feed-water for purified water preparation plants.

Process water must be equal to or better than the standard achieved for potable water. Since one of its uses is in finished products (APIs), the relevant standard will depend not only on the country in which it is being used, but also any potential export markets.

Purified water

Purified water is the output of water purification plants, using ion exchange, reverse osmosis (RO) or distillation. It is used for the manufacture of non-sterile pharmaceuticals, for the preparation of laboratory reagents and test solutions, and as the final rinse water for equipment that will come into contact with non-sterile product.

Once again, the microbiological standard is defined by the pharmacopoeia. The WHO guideline is 50 cfu/ml with an absence of pathogens. The European pharmacopoeia quotes an action limit for purified water of 100 cfu/ml. There is no microbiological limit quoted in the United States Pharmacopoeia (USP). However, the FDA reference document *Guide to Inspections of High Purity Water Systems* states that an inspector would find an action limit of >100 cfu/ml to be unacceptable.

Water for injections (WFI)

WFI is officially called 'water for injections' in European standards and 'water for injection' in the USP. It is generally produced by distillation, although the USP also allows RO as an acceptable preparation method. It is used in the manufacture of parenterals and for the final rinse of equipment that comes into contact with sterile products.

The WHO guideline for WFI is 10 cfu/100 ml with an absence of pathogens and also an absence of pyrogens. The European pharmacopoeia quotes an action limit for purified water of 10 cfu/100 ml. Again, there is no microbiological limit quoted in the USP. However, the same FDA reference document *Guide to Inspections of High Purity Water Systems* states that an inspector would find an action limit of >10 cfu/100 ml to be unacceptable. In other words, in the cases of both purified water and WFI, the

microbiological standards are tacitly, if not officially, the same in Europe and USA. Both standards require a pyrogen level of <0.25 endotoxin units per millilitre.

It should be noted that all these specifications refer to water in bulk. There are a number of other specifications for a variety of types of packaged water, depending on the intended use.

13.3 Design of water treatment systems

There are many options available to companies that wish to install a water purification plant. The decisions taken on design are based on a number of variables.

The specification of the feed-water that has to be treated

This has particular relevance in choosing the pre-treatment stages. It is important that any information relating to feed-water specification is considered over a 12-month period to ensure that any seasonality is recognized.

The balance between capital investment and ongoing running costs

Some of the methods are capital-intensive to install, but can be run cost effectively; others are low cost initially, but have high running costs.

The importance of reducing waste water

This is particularly relevant in regions that have a shortage of water, such as the Middle East or Africa.

Grade of water required

Most factories require a mix of qualities in varying quantities. In some cases, a single system will satisfy all requirements. However, on other occasions, it may be necessary to install a hybrid system or more than one stand-alone system.

The demand profile

It is not enough to know how much of each type of water will be required. It is important to understand the profile of demand; in other words, what will the daily off-take be and will it be a smooth demand with time (unlikely) or will there be certain times of the days when demand will peak (such as the start of the day, when manufacturing is taking place, or late in a shift, when cleaning is taking place).

The ability to manage downtime

Most water treatment plants require time off-line for regeneration or backwash. In a one- or two-shift factory, these operations could be scheduled outside normal working hours. However, for a factory that is operating 24 hours per day (as is often the case in API manufacturing facilities), this is not so easy. In this case, continuity of production would require the system design to have extra capacity, duplicate equipment or buffer storage.

The various stages and types of water treatment are described in the next three sections, with particular reference to microbiological aspects.

13.3.1 Water pre-treatment methods

Filtration

The first step in pre-treatment is often one or more coarse filters to remove particulate matter of >50 µm and to reduce greatly the level of particulates of >10 µm. Sand or multimedia filters are generally used in these stages. It is possible to purchase filters with disposable elements. However, if the raw water is known to have a high particulate contamination, which will lead to the filters blocking up quite quickly, it would be better to install a regenerative system.

These filters are susceptible to microbial contamination and formation of biofilm. If not properly managed, this can lead to higher levels of micro-organisms after the filter than before it. Hence careful monitoring and frequent sanitization are required.

Organic scavengers

Carbon filters are often used in the pre-treatment of water, to remove organic and oxidizing chemicals. This is particularly important if there are high levels of dissolved organic matter in the raw water supply. If this step in the pre-treatment is not effective, the anion resins in the deionizer will quickly become fouled. Once again, microbial growth and biofilm are risks against which precautions have to be taken.

Chemical treatments

During pre-treatment, it is also common to add chemicals to the water for a number of purposes. One of these is the control of microbiological contamination, which is carried out using sodium hypochlorite, chlorine, ozone or hydrogen peroxide.

In many cases, the municipal supply of water will already have been chlorinated to ensure that it achieves potable quality. However, if the residual chlorine level at the point of supply is <0.2 ppm, it may be necessary to carry out further chlorination on-site. The effectiveness of the process will be affected by the pH of the water, concentration of the chlorine and residual time. It is important to determine the effect, if any, of residual chlorine on the final product and to design the system accordingly.

Water softeners

Water softening is often carried out in hard water areas, during pre-treatment in order to reduce the load on the purification units further downstream. This is achieved with base ion exchange, which replaces calcium and magnesium ions with sodium ions. The resins are once again a major source of microbiological contamination and need to be monitored and controlled. As an alternative to putting this process into the main water treatment system, it can be used in specific locations such as the feed-water to boilers or RO units.

Specific treatments

Since all raw water specifications differ, all water treatment systems will also differ. In order to protect purification equipment or to produce the higher quality treated process water, it may be necessary to target specific contaminants. Treatments required could include clarification, ozone treatment, carbon absorption, organic scavenging and deionization. Such techniques may be used singly or in combination, to remove specific problem contaminants including organic matter, colloidal particles, and dissolved iron.

13.3.2 Preparation of purified water

The selection of the appropriate equipment for the preparation of purified water will depend on the quality of the raw water, which would normally be fed from the process water plant and on priorities as determined from the design issues reviewed above. There are a number of equipment options available.

Carbon filters

Carbon filters are frequently used to protect deionizers from dissolved chlorine and from modest concentrations of dissolved organics.

Where possible, disposable cartridge-type activated carbon filters should be used. These must be regularly discarded and replaced to suppress bacterial growth. In large installations, regenerable carbon beds may be used, provided they are regularly regenerated and sanitized (see Section 13.3.7).

Reverse osmosis (hyperfiltration)

Where process water contains high levels of dissolved organics, RO is very effective in reducing these, although such plants require careful specification and operation.

Water is fed at high pressure across a semi-permeable membrane. Some of the water (the permeate) passes through substantially free from dissolved organics (including pyrogens) and bacteria. Some ionic species are also partially retained by the membrane. The residue (retentate) is a more concentrated solution of the original contaminants that is flushed continuously to drain.

The feed-water should not contain significant quantities of suspended solid and colloidal matter (silt). In some hard water areas, some organic species may salt out on the membrane surface. Good pre-treatment of the process water supply to capture and remove all these will help to prevent fouling and the consequent performance loss. Even so, membranes will require frequent chemical cleaning and sanitization to restore performance and subdue bacterial growth.

Membrane selection will normally be on the advice of a specialist supplier. It is important to establish operating limits and performance guarantees for the membranes with respect to temperature, pH, chlorine levels, silt, hardness, etc.

Disposal of the retentate stream must also be considered. This can be a significant effluent volume and there are several ways of dealing with it.

Deionization

Deionization involves passing water over a resin bed, which exchanges metal ions and dissolved salts in the water for hydrogen and hydroxyl ions. The resin has a finite potential for ion removal, which means that the performance of a bed will deteriorate. Resins are regenerated chemically using acids and alkalis.

Resin selection will normally be based on vendor recommendation. The possible effect of non-ionic contaminants on resins should be examined. The system should also prevent carryover of resin fines into the output water. The design should ensure that feedwater chlorine levels do not adversely affect resin performance.

Most systems will consist of two ion-exchange units used in series as described later, with the first system taking out most of the contaminants and the second system polishing the output of the first.

Twin-bed deionization units

These units are generally recommended for the initial deionization duty, or any application where frequent regeneration is likely to be required. They consist of two columns in series, one removing cationic contaminants and the other removing anionic contaminants.

The conductivity of the output must be measured continuously. During equipment qualification, an appropriate cut-off point must be defined to initiate regeneration of the bed. Microbiological build-up inside the columns can be expected. A maximum safe interval between regenerations must be established. It is preferable that the entire regeneration initiation control is automatic.

Purified water should be used to flush the resin beds after regeneration. This reduces the time needed to restore good water quality.

Proper consideration must be given to the handling, storage and use of regeneration chemicals. In particular, the design should ensure that the purified water storage and distribution system is suitably isolated from the column whilst it regenerates.

Mixed resin beds

These beds contain both anion and cation resins. They are recommended for polishing applications where the ionic loading of the feed is relatively low. Performance is monitored by comparing the conductivity at the outlet with that at the inlet. From a chemical point of view, several months of operation can be expected without regeneration. However, during this time, bacterial growth may be expected. Microbiological monitoring is an essential part of establishing and checking the safe interval between regenerations.

The regeneration of a mixed resin system is more complex than a twin bed. Cartridge-type systems are recommended. Cartridge exchange must be controlled to avoid the risk of contamination during and after changeover. *In-situ* regeneration should only be considered in large volume systems.

Electrodeionization

In recent years, alternatives to classical ion-exchange processes have emerged. Just over ten years ago continuous electrodeionization (CDI) was developed in the USA to produce purified water without the problems or costs of chemical regeneration.

The CDI system uses ion-exchange membranes, ion-exchange resins and electricity to produce a consistent quality of purified water. Water enters the unit and flows inside the resin/membrane compartments where the resins capture dissolved ions. By the application of an electrical potential, captured cations are driven through cation membranes and captured anions through anion membranes. The cation permeable membranes transport the cations out of the concentrating compartment, but prevent anions from leaving. The anion-permeable membranes transport anions out of the concentrating compartment, but prevent cations from leaving.

These units are normally used for polishing water supplied from an RO unit, removing carbon dioxide, silica and total organic carbon. Although there is a waste stream from the unit, the recovery is in the order of 80–90 per cent.

Ultraviolet radiation

Ultraviolet (UV) radiation, predominantly at 254 nm wavelength, has the capability of reducing bacterial loading. Provided bacteria are exposed to sufficient UV energy for a

sufficient time, they will be killed. The performance of a UV unit is, therefore, dependent on the intensity of UV, the residence time of water within the unit and whether bacteria can be shadowed by other contaminants.

UV lamps are particularly useful for controlling the bacterial loading in cold recirculating purified water systems. It should be noted, however, that by killing bacteria, the UV process could add to the level of pyrogens in the water and increase the dissolved carbon dioxide levels.

The UV lamp system must be sized to achieve the required residence time at the maximum anticipated flow rate. A UV lamp has a finite life and, therefore, must be fitted with an intensity meter and subjected to an appropriate monitoring programme, to ensure that a fall off in performance is detected before an unacceptably low level is reached.

Use of UV will not alter the need for the system to be periodically sanitized.

Ultrafiltration

This is a mechanical method used primarily to remove bacteria. It is frequently positioned as the final stage of the water treatment plant. Pore sizes vary between 0.22 µm and 10 µm.

13.3.3 Preparation of WFI

The production of WFI and, indeed, the storage and distribution (see next section) requires careful attention to detail, from design through to performance qualification. In general, the simpler the design concept, the more reliable the resulting system.

WFI will normally be produced from purified water using a distillation unit. All the previous methods are part of the process of producing purified water. Distillation is generally used only to produce WFI, although in some countries, it is still a common methodology for producing purified water.

There are three different types of still available: single effect, double effect and vapour compression. Each type results in thermal vaporization, mist elimination and condensation. It is an effective method for removal of chemicals, bacteria and pyrogens.

Water stills should be purchased as packaged plant items from vendors with a good track record of supplying such equipment to the pharmaceutical industry. The still should be purchased complete with all associated instrumentation and controls necessary for safe, effective and reliable operation in accordance with GMP. The design should be assessed paying particular attention to a number of items as discussed below.

Feed-water quality requirements

This relates particularly to chloride content and microbiological quality. Purified water should be used. This provides the best means of ensuring consistent production of WFI quality water and protecting the still from corrosion.

Contamination risks

It is important to ensure that measures are provided to prevent carryover of droplets or particles into the WFI condenser. Measures must also be provided to prevent contamination of the WFI by the heating and cooling media. Heat exchangers should be designed to the double-tube sheet principle.

Energy efficiency

Multiple effect and vapour compression stills are highly energy efficient. The payback on the higher initial capital cost should be assessed. The WFI should be delivered to hot storage at 80°C minimum, which may require the WFI to be heated between the still and storage tank.

Location

The still and storage tank should be located in a technical area dedicated to manufacturing services. The equipment should be arranged so that WFI flows by gravity from the still to the storage tank. Access must be provided for periodic inspection of the internal condition of the still.

Control system

The control system should be arranged to reject any poor quality water. The initial production should be rejected for a predetermined time at every start-up. Any high conductivity water produced must also be rejected. Ideally, the still should self-drain when not operating, to minimize the potential for bacterial growth. Blowdown control should be provided to prevent the accumulation of corrosive contaminants.

Sterilization

Stills with a self-sterilization cycle should be carefully assessed. Some stills are also capable of generating clean steam for sterilizing the storage and distribution system.

13.3.4 Storage and distribution of process water

Process water distribution systems must not be used to supply water for human consumption. Where raw water is treated on-site for both domestic and process use, the design must ensure that there are air breaks between process and domestic systems, and that all local drinking water regulations are complied with.

The distribution system will typically consist of a storage tank and distribution pipework running at ambient temperature. Distribution can be effected by gravity feed where possible, or by a pumping system. Unless the process water is protected against bacterial growth, frequent draining and sanitization will be necessary.

Storage tanks

Tank volume will be determined by the level and variability of demand, supply security, and any need for treatment system downtime. Tank volume should not grossly exceed that required for normal operation. If possible, the tank working volume should ensure a mean residence time of less than 24 hours, to avoid depletion of chlorine levels and resultant microbial contamination and build-up of biofilm. The tank must be capable of complete draining.

Storage tanks must be closed, with vents and overflows protected from ingress of water spray, fumes, insects, birds and vermin. Any reduction in vent area caused by such protection should be accounted for when sizing the vent pipework. Storage tanks must also be capable of regular sanitization. Any chemical sanitization operation must be designed to ensure that the process water cannot be contaminated by sanitization chemicals. Process water storage tanks must not be interconnected with other water systems.

It is recommended that storage tanks are constructed from opaque polypropylene, glass reinforced plastic (GRP) or plastic-lined steel. The tank design should be free from crevices.

Distribution system

All pipework must be capable of sanitization. It must either be self-draining or capable of being flushed to drain. Stagnant areas must be minimized.

Welded polypropylene or high-density polyethylene pipework is preferred for underground systems. This may also be used on pipe-racks or inside buildings provided it is continuously supported. Alternatively, steel pipes with polypropylene or polyethylene lining may be used. Copper tubing may be used for small diameter off-takes within buildings.

Pumps must be of the centrifugal type with single mechanical seals without external seal lubrication.

Use points and sample points

Use points must be designed to minimize any potential for back-flow. Where possible there should be an atmospheric break between the distribution system and the point of use. Provision should be made for periodic flushing and sanitization.

Sample points should be provided such that a representative picture of water quality throughout the distribution system may be obtained.

Control systems

Generally, water systems are not subject to detailed operator attention. The control system should ensure that any out-of-control situations are notified to system engineers as soon as possible.

Equipment requiring backwashing or regeneration will often be supplied with its own control system. Monitoring and alarming of suitable parameters should be considered, to ensure that correct operation of these functions could be verified. For example, monitoring the pressure drop across a filter will allow verification of the backwashing operation, and trending of inlet water particulate loading.

It is recommended that instrumentation be installed to allow the facility's usage of process water to be measured. Appropriate monitoring of individual accountability zones is also recommended.

13.3.5 Storage and distribution of purified water

Storage tank

The tank volume will be determined by operational considerations, i.e. the need to buffer against demand fluctuations and regeneration/cleaning of purification equipment. A sterilizing grade hydrophobic vent filter must be fitted and precautions taken to prevent waterlogging (e.g. heating).

The tank should be designed for full vacuum and overpressure. Sources of overpressure should be evaluated to determine whether a modest design pressure (e.g. up to 4 barg) would be sufficient to avoid the use of an overpressure protection device. If, however,

such a device is needed, a bursting disc, not a pressure relief valve, should be used. A stainless steel non-fragmenting disc fitted with integral rupture detector should be used. Initiation of relief triggers an alarm.

The tank design and operation must minimize static areas and cold spots where bacteria can lodge and multiply. Surfaces should either fully drain or be flushed by water re-entering the tank from the return loop. The level in the storage tank should be displayed.

Distribution system

Ideally, the distribution loop of the water system should be recirculatory, with a feed pipe back into the storage tank, or even back into one of the units of the purification system. In this way, the water is continuously moving, even when none is being drawn off the system at any of the outlets.

It is even better if the water is circulated at an elevated temperature (75–80°C). Some systems circulate at temperatures of between ambient and 60°C, with an occasional increase in temperature to reduce the bioburden.

If recirculation is carried out at ambient temperatures, it is necessary to review the pattern of usage of the water. From experience, systems with ambient circulation and relatively low water usage develop problems with heat gain within the system. In such cases, the actual circulation temperature is closer to 37°C, which is an ideal medium for bacterial growth.

All pipework should be sloped to allow self-draining, and must be capable of chemical or thermal sanitization. There should be no dead-legs in the system, i.e. points where water may be stagnant. These are sometimes found at outlets, if the arrangement of valves is not correct. In some texts, it is stated that a dead-leg should be no more than six times the diameter of the pipe, and there is a mistaken view in some companies that this applies to all systems. However, this rule is only really valid in systems where the water is recirculated at an elevated temperature.

Filters should generally not be used in ring systems, as they provide a breeding ground for bacteria and can mask upstream problems.

The recirculation system should achieve a pipe velocity of between 0.6 and 3.0 m/s, under all usage conditions. Flow must be turbulent.

Pumps for purified water recirculation should be of centrifugal type, of sanitary design and drainable. The shaft seal should be of the single mechanical type. External seal lubrication must not be used.

Pipework must be welded in preference to clamped joints. However, pumps, filters, vessel connections and instruments should be installed using clamp fittings, to allow for maintenance.

Heat exchangers for purified water must be constructed so that there is no seal that has purified water on one side and service fluid on the other. Use of a double-tube sheet exchanger, jacketed pipe exchanger, or a plate exchanger with a double gasket arrangement is acceptable when there is a permanent flow. If either seal should fail, it must be readily detectable. It should be noted that the FDA has expressed a marked preference for double-tube sheet types and is suspicious of plate exchangers.

If a heat exchanger is sited without a continuous flow of purified water, it should be self-draining and capable of daily sanitization. It is unlikely that a plate heat exchanger could meet these criteria.

Use points and sample points

Use points must be designed to minimize any potential for back-flow. Where possible there should be an atmospheric break between the distribution ring and the point of use. If this is not possible, then connections must be demountable and capable of regular sanitization. All user points must be capable of being sampled and must be uniquely identified. Additional sample points should be provided as required for checking water quality

Control systems

Most purification equipment items can be purchased with an independent control system. The integration of these systems will generally consist of providing a centralized alarm system and start/stop signals.

The conductivity of water leaving the purification system should be monitored continuously, with a suitable alarm to indicate system problems. The calibration of conductivity meters should be discussed with the suppliers, as this can be problematic.

If UV lamps are in use, their performance should be monitored by a photometer and run time totalizer.

It is recommended that instrumentation be provided to ascertain the facility's usage of purified water. To minimize the risk of contamination, this is best achieved by measuring the flow of water into the deionizers. Sanitary pressure gauges must be installed where appropriate. The gauge side of the diaphragm must be filled with a food-grade substance acceptable to the regulatory authorities.

In hot recirculatory systems, the temperature should be monitored at the coldest point in the system.

Materials of construction

Ideally purified water should be stored in 316L stainless steel tanks and distributed in stainless steel pipework. However, because of the high costs involved, companies are looking at alternatives for the pipework in particular. In some systems, where it has been determined that polypropylene, PVDF or ABS are acceptable, they may be used as an alternative. However, it is important that construction is controlled to ensure crevice-free, full-bore joints and well-supported sloping pipework.

Polyvinyl chloride (PVC) distribution systems are not recommended. They are difficult to support and deteriorate rapidly. All materials of construction must comply with GMP requirements for materials of contact and be capable of withstanding repeated sanitization by steam or hot water. Any solvent residues present from the plastic pipe jointing process must be flushed out. If non-metallic pipework is installed, it should be designed and installed for chemical cleaning and sanitization with an appropriate solution such as sodium hypochlorite or hydrogen peroxide. The design must allow complete removal of the cleaning and sanitization chemicals by flushing to drain. Valves must be of the PTFE diaphragm type with crevice-free construction, mounted to ensure complete self-draining.

The process of ion exchange involves the use of acid and alkali regenerants. Most deionizing equipment is supplied in PVC, polypropylene or ABS. Screw fittings must not be used; solvent or heat welds should be specified.

Suppliers should be investigated with respect to construction techniques and standards. Sample joints should be requested, to assure the quality of the jointing mechanism. Cleaning operations carried out should be documented by the supplier.

Reverse osmosis systems utilize high pressures to achieve separation. The safety aspects of this should be addressed, and maintenance procedures should ensure that safety features are not compromised.

Insulation

Hot purified water systems must be fully insulated to conserve energy and minimize cold spots. The quality of insulation and cladding should accord with the company standards and be appropriate to the quality of the area.

13.3.6 Storage and distribution of WFI

The production of WFI will generally be achieved by a packaged unit purchased from a specialist supplier. The storage and distribution of WFI demands more detailed investigation and design on the part of the engineer. The design, manufacture and installation of all elements are of critical importance to the satisfactory performance of the system.

For WFI systems, it is generally the case that the storage and distribution system is recirculatory and at elevated temperatures (>80°C), unless the water is going to be freshly made and not stored. A system that operates at <80°C will require regular sanitization and will not allow storage of WFI for more than 24 hours. Such a system should only be used in a laboratory application, or for a single isolated manufacturing use.

It should be noted that water at 80°C represents a potential hazard to operators. The system design should be reviewed to minimize any risk of injury.

The entire system must be equipped for sterilization with steam and must, therefore, be pressure rated. A clean steam supply should be used to achieve this.

Storage tank

WFI storage tanks must be capable of steam sterilization. This will require the tank to be pressure rated (sterilizing steam pressure plus a design margin and full vacuum). As with purified water storage tanks, sources of overpressure should be evaluated to determine whether a modest design pressure increase, e.g. up to 4 barg, could avoid the use of an overpressure protection device. Tank pressure relief must be installed such that initiation of relief is readily detectable and alarmed. A bursting disc with integral rupture detector is preferred. Pressure relief valves are not recommended. A stainless steel non-fragmenting disc should be used.

The WFI in the storage tank must be maintained above 80°C. All WFI entering or re-entering must also be above 80°C. The operating temperature must be high enough to ensure that the coldest point of the recirculation loop will be above 80°C. Heat should be applied either by a heat exchanger in the recirculation loop or via a jacket on the storage tank. The selection should be made after consideration of the operational and design features. Tank jackets are non-invasive, but require tanks to remain substantially filled at all times. External heat exchangers are useful when it is necessary to reheat the water in the recirculation loop.

The tank must have a hydrophobic 0.2 µm vent filter installed. The vent filter must be capable of sterilization when fitted. Precautions should be taken to ensure that condensate does not build up in the filter housing (e.g. by heating the filter).

The tank design and operation must eliminate static areas where water can lodge and cool. Bacteria can multiply in such areas. The entry of the recirculation loop to the tank may be fitted with a spray device to flush all parts of the tank continuously above the water level. This will also provide a back pressure to the recirculation loop.

Distribution system

Filters must not be installed in the WFI recirculation system, since they constitute an area where microbiological contamination is concentrated.

Pumps for WFI should be of centrifugal type, of sanitary design and drainable. The shaft seal should be of the single mechanical type. External seal lubrication must not be used. A standby pump should be available at all times for key applications. It is recommended that the standby pump is not permanently installed, but is kept available for speedy changeover. If the standby pump is installed, precautions should be taken to ensure there is no danger of contamination or dead-legs resulting. Changeover should be in accordance with written procedures and be fully validated. The pump must be steam sanitized before use.

Pumps and piping must be sized to achieve a pipe velocity of between 0.6 and 3.0 m/s under all operating conditions. Flow must be turbulent. Calculations and pump performance data must be documented to form part of the specification and installation qualification. It will be necessary to demonstrate that these velocities are being achieved in practice during operational qualification. None of the available sanitary designs of flow meter can be used with WFI because of its low conductivity.

The pipework must be sloped to ensure that the system can be completely drained. A minimum fall of 1:100 is recommended. Drain points should be provided at sufficient intervals around the ring main. The system must not have any dead-legs.

Sanitary clamped connections should be used to connect pipework to the tank, pump(s), and other major equipment items. Where possible, connections to use points should be physically disconnected when not in use. All other connections must be welded.

The pipework must be equipped for sterilization with steam. Clean steam should be used. Consideration should be given to the introduction of adequate steam and the removal of condensate and air, to allow sterilizing conditions to be reached at all points of the system.

Consideration must be given to methods of providing evidence that sterilizing conditions were obtained, e.g. systematic identification of cold spots during operational qualification, followed by temperature logging during sterilization. Particular problems are encountered in clean areas with flash steam from condensate removal during steam sterilization. It may be necessary to declassify clean areas during the steam sterilization of the WFI system.

Where flow restrictors are used, it is important that correct installation can be verified, and that any failure is readily detectable.

Fixed pipework should be clearly labelled to indicate the contents and direction of flow.

Heat exchangers

The points to be considered for heat exchangers are similar for WFI and for purified water. Heat exchangers for WFI must be constructed so that there is no seal that has WFI on one side and service fluid on the other.

Use of a double-tube sheet exchanger, jacketed pipe exchanger or a plate exchanger with a double gasket arrangement is acceptable when there is a permanent flow. (If either seal should fail it must be readily detectable.) It should be noted that, as for purified water, the FDA has expressed a marked preference for double-tube sheet types and are suspicious of plate exchangers.

If a heat exchanger is sited without a continuous flow of WFI, it should be self-draining and capable of daily sanitization. It is unlikely that a plate heat exchanger could meet these criteria. The use of ordinary shell and tube or plate heat exchangers with single seals and monitored pressure differential between the WFI and utility streams is not acceptable.

Use points and sample points

Generally, the greatest potential for contamination of a WFI system is via its use and sample points. Where feasible, there should be an air break between the ring and the equipment requiring water. Where this is not possible, connections must be demountable and self-draining. The connection should be capable of regular sterilization and should eliminate the potential for back-flow into the ring.

Every use point must be capable of being sampled. When equipment is directly connected to the distribution system, a sample point must be provided. All use points must be uniquely identified.

Equipment items, such as component washers, often have internal valves used to control water flow, which can lead to potential dead-legs when closed. Careful study of the equipment installed at use points is required, to ensure that it does not jeopardize the integrity of the ring.

The design and operation of sample points is of critical importance in obtaining a representative sample and avoiding contamination either of the sample or of the system. Also, the hazards associated with sampling hot water should be made clear and appropriate warning signs fitted.

Routine sampling need not be performed aseptically, since any airborne bacterial contamination can be identified as such and their presence in the water discounted.

Monitoring and control systems

There are a number of critical parameters that must be continuously recorded and alarmed: temperature in the storage tank; conductivity and temperature of WFI at still outlet; temperature of recirculation loop at the coldest point; and conductivity of the still feed water.

The distillation unit should have adequate instrumentation to ensure that an alarm is raised when the still shuts down abnormally, and that basic troubleshooting can be carried out quickly, without the need for additional equipment.

Loss of flow in the recirculation system should be detectable. However, the resulting fall in temperature in the loop is usually a sufficient indicator.

Diaphragm pressure gauges of sanitary design only should be installed on the ring, to ensure that pump performance can be determined. The gauge side of the diaphragm should be filled with a food grade fluid. The diaphragm must be of an approved material, such as 316L stainless steel. The number of gauges should be the minimum necessary for effective operation.

Measurement of the approximate level or weight in the storage tank should be provided.

In instances where heated vent filters are used, it may prove useful to monitor the temperature of the housing to forewarn against condensate build-up that could block the vent.

Materials of construction

All metallic parts that come into contact with WFI must be constructed from 316L stainless steel or a near equivalent. Valves must be of the diaphragm type with crevice-free construction, mounted to ensure complete self-draining. Gaskets and valve diaphragms, etc. must be of materials acceptable to the regulatory authorities, capable of withstanding continuous use at 80–95°C and repeated sterilizations at temperatures up to 140°C.

Pipework should be in 316L stainless steel, internally electropolished. The storage tank, pumps and any other equipment items should have a finish in keeping with the pipework specification.

Ambient systems

Applications where WFI is required at temperatures below 80°C present additional challenges. In considering potential solutions, it is advisable to retain simplicity as a design concept.

Ideally, WFI should be stored at high temperature and only be cooled as it is used. The siting of heat exchangers should ensure that the additional potential for bacterial growth is kept to a minimum. WFI should not be allowed to re-enter the storage tank at <80°C.

If all use points require ambient WFI, a cooler can be installed in the ring, with a heater on the return leg. The section of line between the two exchangers could then run cold when water is required, returning to >80°C at all other times. Frequent or protracted cold operation will require careful design and validation.

If there is a variety of temperature requirements, heat exchangers may be installed external to the distribution ring. In these cases, it is important to either keep a permanent flow through the heat exchanger, or sanitize the exchanger each time before use.

Insulation

WFI systems must be fully insulated to minimize cold spots, conserve energy and protect personnel. The quality of insulation and cladding should accord with national standards and be appropriate to the quality of the area. A good external finish is an important attribute, and of critical importance where pipes pass into clean areas.

13.3.7 Monitoring and maintenance of pharmaceutical water systems

Once a company has invested significant time and money into the purification of water to the appropriate grades, it is important that the quality level is maintained throughout its period of storage and distribution prior to use. During validation, a wide range of tests would be carried out in order to establish the normal profile for the water. These results can then be used to determine what the routine tests should be.

For potable and process water, tests are used that are appropriate to the standard that is being applied. If the water is potable when it comes from the metropolitan system, it

should be possible to obtain some information from the authorities. If no such information is available, it may be necessary to do some testing in-house.

Providing the materials of construction are suitable, there is very little risk of chemical recontamination of purified water or WFI. There are a number of standard tests carried out for measuring the chemical aspects of the water, which are the same for both grades of water. These are not covered here, but may be found in the original pharmacopoeial monographs. On the other hand, the possibility of microbiological recontamination is very real and a great amount of effort goes into preventing this.

For purified water and WFI, there are differences in the microbiological approach, just as there are differences in the standards to be achieved for each grade.

Validation of purified water treatment systems

A water treatment system is different from other equipment used in the manufacture of pharmaceuticals because it has much greater validation requirements. Owing to the seasonality factor of raw water supply, the system cannot be said to be completely validated until 12 months' worth of data are available. Hence, in addition to the IQ (installation qualification) and OQ (operational qualification) stages, there is a 52-week PQ (performance qualification) stage, which can be divided into two phases with different sampling requirements.

Sampling of purified water

During phase one of validation, all points are sampled and tested daily. This phase lasts for between two and four weeks. During phase two (weeks 5–52), weekly samples should be taken from the system feed-water, after every stage of the purification system and on the return loop. Daily sampling is required on at least one user point per day, with the whole system being covered weekly. These results can then be used to set routine monitoring schedules (Table 13.1).

Table 13.1 An example of a routine monitoring schedule

Sample location	Microbiological sampling and testing	
	Phase 1 Weeks 1–4	Phase 2 Weeks 5–52
System feed water	Daily	Weekly
After each stage of purification	Daily	Weekly
At each point of use	Daily	At least one point daily
Return	Daily	Weekly

Sampling of WFI systems

Since a WFI system operating at elevated temperatures is essentially self-sanitizing, frequent sampling is unnecessary. For points of the system where temperature is known to be maintained at >80°C, monthly sampling should be sufficient. Emphasis is placed instead on temperature monitoring and control.

For any points within the system that are subject to reduced temperature, more frequent sampling is recommended.

Samples for endotoxin measurement should be taken from each user point every day that batches of product are being produced.

Microbiological limits

Microbiological limits are indicators of the need for some action to bring the quality of water back under control. They are not intended as accept/reject criteria, either for the water or for the batches of product produced with that water, so long as all product specifications are met and there is a demonstrated compliance to GMP.

For ease of operation and to ensure that a system remains operating at optimal conditions, companies should set three levels of limits:

- Target limits – limits that are known to be attainable with the current technology. For example, a much tighter limit could be considered with a hot system than with a cold one.
- Alert limits – limits that, when exceeded, indicate that a process may have drifted from its normal operating range. Contravention of alert levels does not necessarily require corrective action.
- Action limits – limits that, when exceeded, indicate that a process has drifted from its normal operating range. Exceeding these levels indicates that prompt corrective action should be taken to bring the process back within its normal operating range. It does *not* indicate the automatic necessity to reject batches of water or finished product.

The action limit will generally be set at the pharmacopoeial level. Determination of appropriate target and alert limits should be based upon consideration of a number of points: the process and product specification tolerances; susceptibility of the product types (preservative efficacy, pH, etc.) based on the most susceptible product to be made; subsequent processing of the finished product; equipment design specifications; and historical and/or statistically based levels of microbiological contamination.

In practice, this would mean that limits for purified water stored in a hot circulating system could be tighter than for an ambient system; limits for water to be used in the manufacture of a semi-solid product without a preservative are likely to be tighter than for water used in the manufacture of semi-solid products, which all contain preservatives; and limits for WFI used to manufacture a parenteral product that will be terminally sterilized would not need to be as tight as they are for WFI used to manufacture parenteral products aseptically.

Monitoring data should be analysed on an ongoing basis to ensure that the process continues to perform within acceptable limits. Analysis of data trends may be used to evaluate process performance. This information may be used to predict departures from established operating parameters – signalling the need for appropriate preventative maintenance.

Methodology

The preferred methodology for analysis of sampling is membrane filtration using 0.45 µm filters.

The sample size for WFI is at least 200 ml and for purified water ‘appropriate to the expected result’. In other words, for low levels of contamination, a larger sample is required than for higher levels of contamination.

Monitoring of filters

Vent filters should be integrity tested to ensure that they are still intact. It is very important to ensure that vent filters are not 'blinded' by water, e.g. condensation reaching the hydrophobic filter. If this happens, it can cause rupture of the filter or collapse of the tank.

Other filters, both the large pore size, such as the sand filters, and the microbiological filters should be monitored to ensure that they are not blocked. This can be done by measuring the pressure differential across the filter. For microbiological filters, an alternative method would be to use validation data to determine a time period after which they should be replaced.

UV lamps should also be monitored in terms of their intensity. Manufacturers recommend a number of running hours after which the lamp needs to be replaced. However, it is also possible to measure the intensity of the lamp, using relatively low-cost meters.

Regeneration

Regeneration is an issue for softeners (brine) and twin-bed and mixed-bed deionizers (chemicals) only. (There is no regeneration required for CDI units.) Regeneration is necessary to remove ions from the resin when it becomes saturated. It can also be a method of sanitization of the unit. The process can be automatic or manual, and the procedure should be set on the basis of information obtained during the IQ phase of validation. For mixed-bed units, used as polishers after the RO units, regeneration frequency might be quite low.

Standard regeneration cycles are 2–3 hours. The problems associated with regeneration are the downtime of the unit (which can be overcome by having dual units in parallel or running the cycle at times when the plant is not running) and the large volumes of chemicals that need to be handled.

It is possible to obtain rapid-regenerating units that have an additional cation polisher after the anion resin bed. They have a shorter cycle (30–40 minutes instead of 2–3 hours). The advantages include space saving, a reduction in the need for water storage, energy saving and the requirement for less resin. The disadvantages include the fact that they are packed beds, which prevent the resin moving during regeneration, and hence the trapped material does not have the same opportunity to wash away. Pre-treatment is much more important for this type of unit.

Sanitization

The storage tank and the distribution pipework must be subject to a written programme of cleaning and sterilization. The frequency of such activity will be determined by the historical results collected during validation and the ongoing QC testing.

Sanitization splits into a number of phases within the system. There is the front-end, pre-treatment stage, where chemical means are used. Up to the point of the carbon filter, there will generally be a level of chlorine in the water that will prevent contamination building up. Hence sanitization of this part of the system will tend to be very rare. However, as discussed later in this chapter, biofilm can be a problem that may need to be tackled.

The second stage is the deionization plant (RO, electrodeionization (EDI)), which is generally sanitized chemically, although there is an example of heat being used in the CDI plant.

The third stage is the WFI plant, which is sanitized by heat. Finally, there is the distribution loop that may be sterilized by either chemicals or heat.

Chemical sanitization methods

Chemical sanitizers may be split into oxidizing agents and non-oxidizing agents. Of the oxidizers, the most commonly used is chlorine, which is the most effective and least expensive option. It is highly effective against biofilm. The standard dosage is between 50 and 100 mg/l and the exposure time should be 1–2 hours.

A similar effect can be obtained with chlorine dioxide, using the same concentration and exposure time. However, this is a corrosive material that needs to be mixed on site and hence should be handled with care. For chlorine or chlorine dioxide, the main disadvantage is that there can be problems with contamination of the output water and the finished product. Hence, an effective removal process is required.

An alternative sanitizer that is growing in popularity is ozone. It is generally dosed at between 10 and 50 mg/l and has an exposure time of less than one hour. Under these conditions, it is between 50 per cent and 100 per cent as effective as chlorine. It needs to be produced on site and dosed continuously owing to its instability. The FDA paper on water treatment systems raises the question of whether there are implications for employee health and safety in its use. However, manufacturers and suppliers of ozone generators state that the exposure likely from this use of ozone is an order of magnitude lower than the maximum safe limit for humans. Ozone, apart from its rapid degradation to oxygen, can be destroyed by UV, which is frequently found downstream of the point where it would enter the system.

A further alternative oxidizing agent is hydrogen peroxide, which is dosed at 10 per cent volume/volume for 2–3 hours. It has no problems with by-products, since it degrades to form water and oxygen. However, its effectiveness against biofilm has yet to be proven.

In addition to the oxidizing agents, there are a number of non-oxidizing agents that can be used. Quaternary ammonium compounds are effective as biocides and surfactants. However, there can be problems in removing them from the system. Anionic and non-anionic surfactants are not particularly effective as biocides on their own, but can be used in conjunction with other compounds to remove biofilm.

Previously, many companies have used formaldehyde as a sanitizing agent. It is relatively non-corrosive to stainless steel and is an effective biocide. However, it is less effective against biofilm and, as it is carcinogenic, it presents significant health and safety issues. Its use is thus being phased out.

Physical methods – heat

Stills supply WFI to the system in excess of 95°C. However, this temperature cannot be maintained without a heat exchanger and heat loss within the system will reduce the temperature to around 80°C. Circulation at this temperature will prevent the proliferation of bacteria. However, a paper by Mittelman (1986) shows that this will only reduce biofilm development.

Therefore, although such hot circulating systems for WFI are essentially self-sanitizing, it may be necessary to sanitize the entire system periodically. This may be achieved by raising the temperature above 121°C for around 30 minutes. This can be carried out by draining the system contents and injecting pure, clean steam and pressurizing to around

2.0 barg. This traditional method is very reliable, but has the disadvantages of the direct expense of extending the pure steam system to the WFI system, and the indirect expense caused through the downtime incurred in removing air from the system and manually fitting steam-trapping equipment. There are also health and safety issues associated with steam.

An alternative to pure steam is to sterilize the system with high-temperature WFI. The system is drained down and a predetermined quantity of WFI is heated by an in-line heat exchanger. When the vessel temperature has reached 100°C, the vessel vent valve is closed and the system starts to pressurize, allowing heating to 125°C. Water at 125°C is circulated around the system for 25–30 minutes.

Whichever method of sterilization is used, it will be necessary to use thermocouples connected to chart recorders to obtain a record of the process.

Recently, work has been carried out on the hot water sanitization of CDI units. It was demonstrated that, with a weekly cycle of 40 minutes warm-up (25–65°C), a hold period of 60 minutes at 65°C and a cool-down period of 40 minutes, effective sanitization was achieved and a three-year life could be expected from the unit. This work is fully described in the paper by Wood, Hirayama and Satoh (2000).

Mechanical scrubbing

Heavy biofilm cannot be removed from storage tank walls by the use of chemicals alone; mechanical scrubbing or scraping, high-pressure spraying, or a combination is also required. However, mechanical removal of biofilm from distribution systems is impractical.

13.4 Biofilm

Water systems exhibit a particular microbiological problem in the form of biofilm. As well as existing as free organisms within the water, bacteria also become attached to the surfaces of the pipes and tanks. This biofilm will act as a form of protection for the individual organisms; however, periodically sections of the biofilm will slough off and increase the microbial level in the water. As a result, contamination levels will not be uniform throughout the system. Under these circumstances, sample results will not be representative of the type and level of contamination across the entire system. Counts of 10 cfu/ml in one sample and 100 or even 1000 cfu/ml in other samples might easily be observed.

The reason that biofilms are such a problem is that they provide protection to bacteria and hence are much more difficult to remove from the water system. Bacteria in this form may be 150–3000 times more resistant to free chlorine and 2–100 times more resistant to monochloramine than free-floating bacteria.

The development of biofilm is independent of the material of the surface. Biofilm will develop just as easily on stainless steel as on plastic. A major factor that aids the development of biofilm is the large surface area that exists within a water treatment, storage and distribution system. All the elements of the system including RO membranes, deionization resins, storage tanks, cartridge filters, and piping systems provide surfaces suitable for bacterial attachment and growth.

Development of biofilm

As soon as a clean tank or piece of pipework is filled with water, a biofilm may start to form. The development of the biofilm occurs in a number of steps as detailed below.

- Surface conditioning: trace organics are deposited at the interface between the water and the walls of the tank or the pipework. This layer neutralizes surface charges and allows the bacteria to be close enough to become attached to the wall. Additionally, the layer provides a source of nutrients for the bacteria.
- Adhesion of pioneer bacteria: free-floating bacteria enter the boundary layer area at the wall where the velocity is virtually zero and become adsorbed on to the walls. The attachment is initially due to physical rather than chemical factors.
- Slime formation: the bacteria within the biofilm produce sticky polymers that hold the biofilm together and increase the adhesion to the walls. The strands of polymer also act as a protective barrier and concentrate any nutrients available in the water. The pioneer bacteria then start to reproduce and thus increase the surface area of the biofilm.
- Secondary colonizers: the slime will then trap other bacteria from the water by physical, electrostatic attraction. These secondary colonizers feed off the waste produced by the primary colonizers and increase the size of the biofilm.
- Fully functioning biofilm: a mature biofilm is living tissue, made up of different bacterial types living as a community. It may even be considered to have a primary circulatory system.

Biofilm continues to develop in two ways. Growth will occur by normal reproduction, which will increase the size of the original community. However, as the thickness of the film increases, it will move out of the boundary layer into areas where the velocity of the water is greater and thus the sloughing off process will occur. Some of these cells will then form other areas of biofilm elsewhere in the tank or the pipework.

The speed of development of the mature biofilm can vary from hours to weeks, depending on a number of variables in the system. In fact it has been observed that *Pseudomonas* cells can start to form a biofilm on electropolished stainless steel surfaces, within 30 seconds of exposure.

A smooth surface may delay the early stages of development; however, in the long run, the overall size of the biofilm does not appear to be reduced by smoothness.

Common misconceptions about biofilms

It was previously thought that biofilms were disorganized associations of cells. Recent advances in microscopy of biofilm has shown that they are in fact highly organized, complex structures.

It was originally assumed that biochemically, there was no difference between free-floating bacteria and those in the biofilm. However, it has been discovered that, although genetically they are the same, owing to a change in the genes that are in use, the biochemical behaviour is actually different.

The biocidal activity of any given disinfectant (CT) is known to be the product of concentration and time. It has been shown that CT values for free-floating bacteria cannot be extrapolated to the bacteria within biofilms.

Biocorrosion

Biocorrosion occurs on metal surfaces as a result of the presence of biofilm. It is exhibited in a number of forms, including pitting, crevice corrosion, selective dealloying, stress corrosion cracking and under-deposit corrosion. It is caused either by oxygen depletion, leading to a difference in electrical potential between different parts of the surface or destruction of the passivation oxide film. Additionally, anaerobic bacteria, such as sulphate-reducing types, are able to flourish in this environment and increase corrosion.

Control of biofilms

The control of biofilms in water treatment systems is very difficult. As free-floating organisms, bacteria do not develop a resistance to biocides, as they do to the antibiotics used in medicine, since there are many potential target sites that can be attacked. However, in the form of a biofilm, there is physical protection from the biocide. If sanitization is not completely carried out, it will only be a short time before the biofilm is fully functional once more.

There are a number of reasons why control of biofilms is very difficult:

- The nutrient levels required are so low that even purified water can provide sufficient food.
- The sticky polymers form such tight bonds that the turbulence within the pipework is not strong enough to break them.
- Even after smoothing the surfaces and removing all crevices in welds, etc., the bacteria are still able to attach themselves.
- The slime forms a physical protection of the bacteria from chlorine or other sanitizers.

In conclusion, the methods adopted by companies will tend to involve a number of different measures and it will be accepted that this will tend to control the biofilms, rather than completely eradicate them.

13.5 Common problems and troubleshooting

From a microbiological viewpoint, there are a number of areas that can cause problems within pharmaceutical water treatment systems. The FDA guideline presents a discussion of some of these areas, by quoting cases that have been found during factory inspections. Some of these are briefly reviewed in this section.

Problems with purified water systems

Problems have been observed with RO systems, since they operate at ambient temperatures and the filters do not retain bacteria. Solutions that are suggested include use of a UV lamp or heat exchangers downstream of the RO unit. In either case, this would reduce the contamination level.

Problems with WFI systems

Problems have been observed more in relation to endotoxin levels than microbial contamination. These have been found to be due to such causes as: feedwater droplets being carried into the distillate; stagnant water in the condenser over the weekend; or

insufficient pre-treatment of feed-water. Since most stills will only result in <2.5 log reduction in endotoxin content, a low level in the feed-water is essential.

Observations of a circulatory system that had been switched off showed that contamination developed within less than 24 hours. This resulted in the FDA recommendation that non-circulating systems should be drained at least daily.

Problems with heat exchangers

There is an FDA Inspectors Technical Guide entitled *Heat Exchangers to Avoid Contamination*, which discusses design issues and potential problems. Contamination owing to leakage can be prevented by using pressure differential monitors to ensure that there is always a higher pressure on the clean fluid side. As discussed previously, use of the double-tube sheet type of heat exchanger is also preferable. Problems can also be seen if the cooling water is drained out of the heat exchanger when it is not in use, since corrosion can lead to pinholes being formed.

Problems with pumps

If pumps are not operational continuously, they should be fully drained, in order to prevent build-up of contamination in static water within the reservoir.

Problems with the distribution loop

Problems that are discussed in relation to the distribution loop include the contamination that can occur when a user point has a hose connection that will contain non-sterile air. Depending on the order in which valves are opened, it can be possible for the non-sterile air to contaminate the rest of the system. The issue of dead-legs is also discussed and the non-validity of the 'six diameters' rule is emphasized for systems that are not held at >80°C.

Problems are also discussed regarding the use of bacterial grade filters in the system, since they can provide a good environment for growth. In addition, they tend to hide any underlying contamination in the system and do not remove endotoxins. If a filter is unavoidable, there must be a written procedure, including the frequency of changing the filter.

The importance of 'cracking' terminal valves during sanitization is stressed, to ensure that all parts of the pipework are filled with water and thus exposed to the sanitizer.

The storage tank is one part of the system where it is hard to maintain high turbulence. In order to minimize the problem, it is recommended that tanks should be sized so that the volume change is 4–6 times per hour.

13.6 Waste water treatment

As the pharmaceutical industry develops products with greater potency and toxicity, and with the growth of worldwide public awareness of the dangers resulting from pollution of the environment, the importance of dealing with waste within the pharmaceutical and chemical industries has taken on a new urgency. In both Europe and the USA, failure to comply with the regulations can have serious consequences for a company. In the context of this chapter, the discussion will centre on the treatment and disposal of waste water.

The treatment of waste water dates back to construction of sewers in the cities of Crete,

ancient Assyria and the areas ruled by the Romans. Towards the end of the Middle Ages, cesspools and underground systems were constructed to deal with human waste.

As the population grew in the nineteenth century and cities started to expand it was recognized that human health would be improved if human waste could be rapidly removed using storm drains. The really significant leap forward in sanitary engineering was the invention of flushing toilets that enabled the development of the modern sewerage system.

During the middle of the twentieth century it was realized that flushing ever-increasing quantities of waste into lakes and rivers caused serious health risks and, as a result, governments started to invest in the construction of central sewerage treatment plants for major centres of population. In addition, legislation was enacted to start the control of liquid and gaseous pollutants.

Measurement of water contamination

The composition of waste water is analysed using several physical, chemical and biological measurements. The main measurements are as follows.

- Biological oxygen demand (BOD): this is the amount of oxygen used over a 5-day period by micro-organisms as they decompose the organic matter in the effluent at a temperature of 20°C. BOD tests the strength of untreated effluent and biodegradable waste in the water.
- Chemical oxygen demand (COD): this is the amount of oxygen required to oxidize the organic matter by using dichromate in an acid solution to convert it to carbon dioxide. COD tests the strength of waste water that is either not biodegradable or contains compounds that inhibit activities of micro-organisms.

The value of COD is always higher than BOD because many organic substances can be oxidized chemically but can not be oxidized biologically. As the terms suggest, BOD and COD combine with free oxygen in the water. In extreme cases, oxygen depletion can cause damage to living creatures in the water.

Other measures include pH and chemical composition.

Treatment of waste water

A pharmaceutical manufacturing plant will produce a variety of waste water streams: domestic sewerage – from toilets, wash rooms and the canteen; process waste water – non-contaminated washing water and process cooling water; contaminated waste water – any effluent that is contaminated either chemically or biologically during the process; and general site drainage – water run off from the site infrastructure.

There are a number of options that can be incorporated in designing a waste water treatment system.

Settle tanks

Settle tanks allow the waste water stream to pass very slowly through a specially designed trough system. Inorganic particles of >0.2 mm fall out of suspension and drop to the bottom of the tank. After removal, these are disposed of in landfill sites or are incinerated.

Sedimentation
This is similar in principle to the settle tank and results in between 40 and 60 per cent of the suspended solids being removed. By the addition of chemicals to the sedimentation, coagulation occurs, which further increases solids removal.

Flocculation
With additional treatment, up to 80 per cent of the suspended solids can be removed, reducing up to 40 per cent of the BOD.

Digestion
This is an anaerobic microbiological process that converts organic sludge to methane and carbon dioxide.

Biological treatment
This is an aerobic process where organic matter is converted to carbon dioxide, water, nitrates and phosphates. The solid waste generated would go to landfill or be incinerated.

Filters
Depending on the contaminant to be removed from the effluent stream, the major filter manufacturers have ranges of products that will be suitable. However, filtration would normally be only one stage in the treatment of the effluent stream.

Advanced oxidation
This is a simple but effective way of treating industrial effluent, using the oxidization power of ozone, which is enhanced by the catalysing effect of UV light (producing hydroxyl free radicals) and destroying the chemical demand for oxygen. The system is a very green solution as not only does it treat the contaminants but it results in a clean discharge stream that is saturated in oxygen.

Macro porous polymer extraction
This is a system that has been developed by Akzo Nobel in the Netherlands using new polymer-based technology for the removal of hydrocarbons from water. It has shown excellent performance in the removal of many of the solvents used in the pharmaceutical industry. The manufacturers claim up to 99.99 per cent removal for the system.

The waste stream is passed through a specially designed column, which is packed with the macro porous polymer. An extraction fluid, immobilized within the polymer matrix, draws the hydrocarbons out of the water. When the extraction fluid is saturated, the column is regenerated by top feeding the column with low-pressure steam, releasing the hydrocarbons, which can be condensed and collected for reuse or incineration.

14

Quality improvement programmes

14.1 Introduction

The last three chapters of the book look at quality in a much wider sense than that addressed previously. They deal with the use of quality management techniques, which are appropriate not just in the technical environment, but throughout all areas of the business. This chapter is essentially a theoretical overview of quality improvement programmes and is probably most relevant to someone who wants to understand the historical context. Chapter 15 deals with practical tools and techniques that can be applied within quality improvement programmes. Finally, Chapter 16 reviews some specific examples of how these activities have been applied within the pharmaceutical industry.

It is impossible to write about quality management techniques without discussing the concept of quality improvement programmes or total quality management. It is within the context of TQM that most of the quality techniques have been used in the past 20 years or so.

TQM is the management of all aspects of the quality of service provided to the customer – not just the product itself. It is recognized by many organizations as one of the most significant factors involved in gaining competitive advantage in business.

14.1.1 Elements of TQM

Over the years, many different types of TQM programmes have been established. However, there are a number of elements that are common to all of them.

Meeting customer requirements

This involves recognizing the exact requirements of the customer (in all aspects of the service on offer) and satisfying them effectively and profitably. Often it is found that one of the problems is that the customer has never fully defined what is required. An agreed specification is essential.

Definition of the customer

The ultimate or external customer is the person at the end of the line who receives the service and uses the product. However, in any organization, there are also many internal customer/supplier interfaces. At each of these interfaces, a specification can be drawn up for the service required.

Prevention not cure

This involves building quality into the system from the start, rather than spending time and money correcting mistakes or inspecting out rejects. (This concept is discussed fully in Chapter 7.)

Zero defects

This is not an impossible ideal – but a very real requirement of customers today. It is hard to achieve, but should be continually worked towards. The only acceptable objective of any activity should be 'right first time'.

Contribution to the bottom line

Doing things right first time is always more cost effective than making a mistake. Hence improvements in quality of service are accompanied by an increased profitability for the organization. (Once again, this is fully discussed in Chapter 7.)

14.1.2 TQM and the pharmaceutical industry

The pharmaceutical industry has always paid more attention to quality than most other industries. There are well-developed quality assurance and quality control functions, regulatory bodies such as the EMEA and the FDA and, in the case of larger companies, in-house guides to GMP and other requirements. It would be tempting to think that TQM would be totally superfluous. However, that is not the case at all.

The aspect of quality considered within the pharmaceutical industry to date is the quality of the product alone. Does the drug do what it is supposed to do – and no more? Is it efficacious and safe? This may be defined as traditional quality.

Total quality differs from traditional quality in at least two areas: firstly, it considers all aspects of the service to the customer, not just the product; and, secondly, the emphasis is a commercial one – quality as a means of gaining competitive advantage.

Total quality does not in any way detract from or compromise the traditional quality focus of the pharmaceutical industry. Rather it seeks to build on the excellence of the product by achieving the same standard within all other aspects of the service to the customer.

14.1.3 Definitions

There are almost as many definitions of quality and TQM as there are books written about the subject. This section provides a few, but is by no means an exclusive list:

In ISO 9000: 2000, quality is defined as 'the ability of a set of inherent characteristics of a product, system or process to fulfil requirements of customers and other interested parties'.

Juran defines quality as 'fitness for purpose', whilst Crosby talks about 'conformance to requirements'. Feigenbaum emphasizes that quality is not an absolute as in 'the best' but relates to 'best for the customer use and selling price'. All these definitions are similar in that they relate to conforming continually to clearly understood and agreed customers' requirements at the lowest overall cost.

An alternative approach is that presented by Macdonald and Piggott – that of 'delighting the customer'. This is also the message given by Tom Peters in some of his early work.

Whatever the chosen definition of quality, TQM can be defined as a strategic approach to producing the right quality of product consistently, through a process of continuous improvement and innovation.

14.1.4 What's in a name?

The term TQM has become rather discredited in some quarters in recent years, owing to problems that have been experienced in some companies with TQM programmes that have failed. The reasons for those failures are various – and some of the possible causes are reviewed later in this chapter. However, as a result, many companies shy away from using the term.

In some cases, alternative labels are applied such as world class manufacturing or business process re-engineering. In other cases, there are no high-profile programmes being run within the company.

However, this is not to say that the overall philosophy of needing to improve the quality of everything that we do, in order to satisfy fully (or even exceed) customer requirements, is an invalid one. It is more a case of the labels or the trimmings getting in the way of the substance.

As a result, many companies are continuing some or all of the activities that were part of a traditional TQM approach, but without labelling them as such. It is as if quality improvement in its widest sense has become incorporated into the normal operation of the business – which is exactly where it should be.

For the remainder of this book, the generic term 'quality improvement' will be used to describe the diverse activities that different companies are carrying out.

14.2 History – the key figures

Throughout the history of quality management, there are many people who have contributed to the thinking and body of literature. However, there are four key figures that stand out above the others. These are discussed below.

14.2.1 W. Edwards Deming

W. Edwards Deming was an American physicist who worked for many years for the US government in the area of statistical sampling techniques. In the late 1940s and early 1950s, Deming spent a lot of time working with industry in Japan, via the Union of

Japanese Scientists and Engineers (JUSE). It was Deming who is largely credited with the introduction and development of statistical quality control within Japan, at a time when the industry in that part of the world had yet to gain its reputation for world class quality.

Variability in processes

Deming's approach was based on a rigorous statistical approach to quality. The key point of his philosophy was the elimination of variations in processes. He identified that variations in a process could be divided into two types: special causes and common causes.

Special causes are defined as the problems that can be attributed to one-off causes, such as operator error or machine breakdown. They can be eliminated by anyone associated with the process, depending on the individual problem. Deming estimated that only 6 per cent of problems are due to special causes.

Common causes are defined as the problems that can be attributed to underlying causes, such as poor-quality raw materials. They can only be eliminated by management action. Deming stated that the remaining 94 per cent of problems are due to common causes.

It is on the basis of these statistical estimates that Deming believed that most problems in the workplace could be attributed to poor management. It was his contention that no one ever does a job badly out of choice.

Deming's philosophy

Deming used statistical tools such as Shewhart control charts; however, he did not contribute new tools to the field himself. His greatest contribution has been in the development of a philosophy that started to change the way industry thinks.

Deming's philosophy was primarily encapsulated in a list of 14 points for management. He believed that they were not set in stone (and in fact, he was continually adjusting them), and they were not a set of rules. They were merely to be used as triggers for changing the way a company thinks. (It should also be mentioned that they do not agree with the philosophy of the other key figures in the field in all points.) The list of points that follows is taken from private notes made during a one-day Deming seminar. The comments after each one are the author's interpretation.

- Constancy of purpose. It is necessary to create constancy of purpose in order to ensure that products and services are continually improved.
- The new philosophy. The responsibility of management to learn and to provide leadership must be appropriate for the economic circumstances of the times.
- Cease dependence on inspection. Statistical measurement should be used to build quality into the product and thus reduce the need for high levels of inspection at the end of the process.
- End 'lowest tender' contracts. The objective should be to minimize total cost and to develop good relationships with single-source suppliers where possible.
- Improve every process. There should be an ongoing drive to improve quality, which leads to higher productivity and lower costs.
- Institute training on the job. Skills need to be continually updated to keep in line with changes in the workplace. This training should extend to managers, to ensure that they use the workforce most effectively.

- Institute leadership. The responsibility of management must be to help the workforce carry out their duties more effectively. Leadership must focus on quality rather than quantity.
- Drive out fear. There should be open, two-way communication across the organization to reduce any feelings of fear that exist amongst the workforce.
- Break down barriers. In all organizations, particularly larger ones, there are barriers that arise between different departments or functions. These barriers must be eliminated and cross-functional teamworking encouraged.
- Eliminate exhortations. Deming believed that poster campaigns, numerical targets (such as zero defects) and exhortations to the workforce to work harder are meaningless, since most of the problems are outside the ability of the workforce to sort out.
- Eliminate targets. Numerical goals tend to focus on quantity rather than quality and hence can be counterproductive. They should not be allowed to replace leadership by management.
- Permit pride of workmanship. By reducing the problems that cause people to produce poor-quality work, there will be a tendency to increase the pride that they feel in the results they achieve.
- Encourage education. The importance of training has already been emphasized. This is an additional point, in that the better educated people are, the more they will be willing and eager to take part in a continuous improvement programme.
- Top management's commitment. Any improvement activity will only last as long as the support that it receives from the senior management of the company. If their commitment is lacking, the programme will wither and die.

Deadly diseases

Deming also identified a number of 'deadly diseases', which he observed to be prevalent in Western management. These need to be overcome if the objective of continuous improvement is to be attained.

- Lack of constancy. Companies tend to fail to plan for the future and maintain programmes on an ongoing basis.
- Short-term profits. The inability of companies to invest in quality for the future, owing to things such as the behaviour of funding organizations, can lead to a short-term approach.
- Performance appraisal. The use of performance appraisals, merit systems and management by objectives can be detrimental if they create an atmosphere of fear and blame within the organization.
- Job-hopping. The tendency of managers, in particular, to move between jobs after relatively short periods of time causes instability in the organization and can result in companies being managed by people who do not know the industry or the company well enough.
- Use of only visible figures. The use of only obvious (primarily financial) measures does not give the whole picture. That is why it is important to use statistics to measure the things that are generally not known.

14.2.2 Joseph M. Juran

Dr Joseph Juran was an American, born in Central Europe. He was an engineer by profession and first became famous with the publication of a textbook on quality control, which included his theory on the economics of quality. It was in this book that he first discussed the concept of the cost of quality (see Chapter 7).

Juran went to Japan in the early 1950s, following in the footsteps of Deming. He also worked with JUSE, but his lectures were also disseminated to more junior levels of management and triggered the development of internal training courses in some of the larger companies.

Juran focused on management much more than process. He believed that quality control is a key part of management control. His emphasis was on planning, organizational issues, management's responsibility for quality, and the importance of setting goals and targets for improvement.

Juran's philosophy

Juran's key message was that quality needs to be planned; it cannot just happen by accident. He defined a quality trilogy of quality planning, quality control and quality improvement. With an emphasis on goal setting and a drive for error reduction, there is some conflict between his work and that of Deming. However, they did both agree on the fact that the vast majority of variations within a process are within the responsibility of management, rather than down to individual operators. In Juran's case, he estimated the level to be over 80 per cent (as opposed to 94 per cent for Deming).

Figure 14.1 illustrates this trilogy, using a control chart. It differentiates between the 80 per cent of variations that provide an opportunity for improvement activities (equivalent to

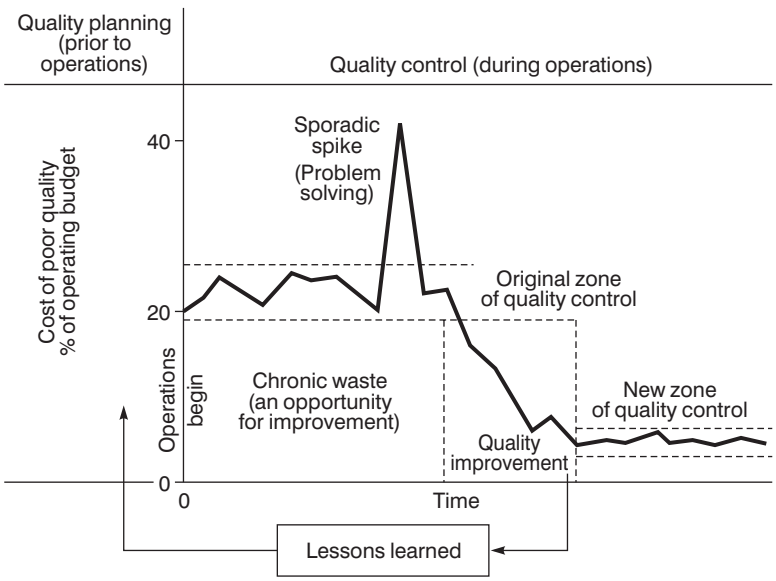

Figure 14.1 Illustration of the quality trilogy via a control chart. (Adapted from Juran on planning for quality, 1988.)

Deming's common causes) from the small percentage of sporadic problems that can be addressed by individual or group problem solving (equivalent to Deming's special causes).

Juran defined a 'quality planning road map' to describe the steps that need to be taken in order to improve the quality of the operation.

- Identify who are the customers. This introduces the concept of both external and internal customers. Every person within an organization is a customer of the preceding person in the process flow and a supplier to the succeeding person. This holds true, not only within a manufacturing environment, but also in other technical areas, such as the QC laboratory, and in the administration areas, such as finance or order processing.
- Determine the needs of those customers. In many cases, this is not just a case of the 'supplier' not knowing what the 'customer' wants. Often, the 'customer' has not defined exactly what is required. With such a lack of clarity, it is not surprising that needs are not satisfied.
- Translate those needs into our language. In many cases, particularly in the case of an external customer, the requirements will be expressed in 'layman's' terms that need to be converted into the more appropriate terminology for the process in particular.
- Develop a product that can respond to those needs. Having defined the needs, it is important that the 'product' – whether it is a physical product or an intangible service – satisfies the requirements of the customer. It must have 'fitness for purpose'.
- Optimize the product features so as to meet our needs as well as customers needs. In order to ensure that the product is both effective (i.e. does the right thing) and efficient (i.e. does things in the right way), it is important to ensure that all stakeholders' requirements are considered, not just the end customer.
- Develop a process that is able to produce the product. It is important that, once the product has been designed, there is a consistent process in place to ensure that the product can be produced to order and on time.
- Optimize the process. Having designed the process that will produce the product effectively, it is then necessary to optimize that process so that it operates efficiently as well.
- Prove that the process can produce the product under operating conditions. Producing a product under special conditions, such as in a test laboratory, is the starting point. However, it is critical that the process will also operate effectively under normal working conditions.
- Transfer the process to operations. Once all the optimization and proof of operation has been carried out, then the process can be transferred to the operations department and full-scale production can begin.

Whilst the above 'road-map' was described in terms of a manufacturing process, the same principles can easily be applied to an administrative operation or any other service activity

It will be observed that this map describes very well the stages that the pharmaceutical industry goes through in order to research and develop a new drug and validate its manufacture before releasing it to the manufacturing department for normal production.

The quality crisis

Juran believed that, whilst many companies from the 1980s onwards developed an increased awareness of the need for improved quality, there was less success when it came

to the need to change behaviour. This failure was attributed to a lack of planning and substance within improvement programmes.

It would appear that the programmes did not progress from the original communications exercise to planning the specific tasks that needed to be carried out nor was there any responsibilities allocated for carrying out those tasks. Thirdly, there was no structured process for carrying out the tasks – the tools and techniques were missing. Finally, there was no reward system for management related to the required activities.

Juran was particularly insistent that training for quality improvement should start at the very top of the organization. However, this view was not well received by many senior management teams who felt that 'it was everyone else who had to learn and change'.

14.2.3 Phillip B. Crosby

Phillip Crosby is an American who spent his early career within quality control before moving into consultancy. Although he agrees that more than 80 per cent of problems need management involvement to be solved, he differs from Deming and Juran, in that his approach majors on slogans, exhortations and getting all the workforce involved in identifying causes of problems.

Although he has not made such a major contribution to the history and body of knowledge of quality management as Deming and Juran, Crosby's name is very well known. His work is known worldwide, but is centred on the USA.

Crosby's philosophy

Crosby's definition of quality is 'conformance to the requirements which the company itself has established'. He believes that most companies expect things to go wrong during any process and hence build in an allowance for these problems. Crosby developed the concepts of doing things 'right first time' and 'zero defects'. He suggests that, if the company does not start off by expecting mistakes (and thereby implicitly accepting errors as OK), quality will be improved.

One of the problems with this approach relates back to the statistic, already stated, that more than 80 per cent of problems within a process are fundamental ones that require management intervention to be put right. It was found that problems were being highlighted by the workforce, but that the management team could not react quickly enough and hence the programme would grind to a halt in disillusionment.

Crosby's four absolutes of quality (plus one)

There are four absolutes of quality that Crosby has defined, together with a fifth one that he added later on. These absolutes are as follows.

- Quality is defined as conformance to requirements, not as 'goodness' nor 'elegance'.
- The system for causing quality is prevention, not appraisal.
- The performance standard must be zero defects, not 'that's close enough'.
- The measurement of quality is the price of non-conformance, not indices.
- There is no such thing as a quality problem.

By comparison with previous sections in this chapter, it can be seen that there is a great similarity between these absolutes and the conclusions of Deming and Juran. The main difference appears in the methods that Crosby recommends for achieving quality improvement.

Crosby's 14 steps to quality improvement

Crosby identifies the following steps that need to be taken in order to improve the quality of the organizational performance.

- Management commitment. It has already been stated that any sort of activity within an organization needs leadership and commitment from top management if it is to succeed.
- Quality improvement team. The use of teams within the quality improvement programme is discussed later in this chapter. It is important that all parts of the organization are involved, in order to establish 'ownership' of the programme.
- Quality measurement. If something is not measured, there is no way of knowing the current situation and hence it is not possible to develop targets for improvement or chart progress towards that target. Crosby encourages the measurement of defects and the posting of charts in the workplace, so that improvements can be monitored visually over time.
- Cost of quality. This concept is fully reviewed in Chapter 7. Crosby emphasizes that this measurement should be available, so that everyone is aware of the price of non-conformance.
- Quality awareness. For a quality improvement programme to have any chance of success, it must involve all members of the organization. Hence any programme should start with a good communications exercise to ensure that everyone understands the purpose and the objectives.
- Instigate corrective action. This requires the identification of problems and the positive action that needs to be taken to ensure that problems are corrected.
- Establish an *ad hoc* committee for the zero defects programme. This would be a cross-functional committee with responsibility for monitoring the zero defects programme, facilitating its activities and publicizing its successes.
- Supervisor/employee training. Supervisors and employees need to be trained in the tools and techniques that are used for problem-solving and corrective action projects. These tools and techniques are discussed later in the next chapter. Additionally, supervisors need to be trained in running and/or facilitating teams.
- Hold a zero defects day to establish the new attitude. This would be a symbolic activity to aid the communications effort and emphasize the message that a change in culture is expected to occur.
- Employee goal setting should take place. This is usually done on a 30, 60 and 90-day basis. It would be tied in to the quality measurements referred to earlier in this list of steps.
- Error cause removal. Once problems have been collected, their fundamental causes are identified and these causes eliminated. As already stated, this will place a heavy load on the management team, to correct fundamental underlying problems that are not attributable to individuals.

- Recognition. Individuals or teams who achieve their goals or perform very well should receive appropriate recognition. Crosby recommends that this should be a non-financial award. (This differs from the traditional suggestion scheme that companies sometimes run, where a financial award is presented, commensurate with the value to the company of the implemented suggestion.)
- Quality council. This is a steering committee for the entire quality improvement programme. It can be made up of a mixture of functional quality specialists and project team leaders.
- Do it all over again. This is recognition of the message, common to all the quality 'gurus', that the journey towards quality improvement is a never-ending one. Every time the process is re-examined, it will be possible to find some way to improve its effectiveness. It is also a recognition of the fact that improvement tends to be brought about by many small incremental steps, rather than a few large strides.

14.2.4 Dr Kaoru Ishikawa

Dr Ishikawa was a Japanese engineer who is credited with the establishment of the quality circle movement in Japan. (Quality circles are discussed more fully in Chapter 15.) He is known both for his development and use of statistical techniques, and also for ensuring that the quality control culture spread throughout the organization within Japanese companies. Participation in quality improvement activities was seen at all levels from top management downwards.

Ishikawa's techniques

Ishikawa emphasized the use of many statistical tools in the determination, evaluation and analysis of causes of problems. Such tools include Pareto charts, control charts and scatter diagrams, all of which are presented in Chapter 15.

However, the tool for which Ishikawa is best remembered – and the one that colloquially bears his name is the cause and effect diagram, which is also known as the fishbone or Ishikawa diagram.

Company-wide quality control

Ishikawa promoted a company-wide approach to quality control, involving all levels of management and the workforce, across all departments of the organization. The methodology was used not only to control materials and activities, but also for problem solving and decision making.

Benefits of this sort of approach were numerous and included:

- improved quality of the product, increased consistency and reliability, leading to reduced costs;
- improved productivity, leading to better planning and reducing inventories;
- reduced appraisal and failure costs; and
- better relationships between functions within the company, and with suppliers and customers.

14.3 Prerequisites for successful quality improvement programmes

Reading the views of the various quality 'gurus' as a prelude to establishing a quality improvement programme could be confusing, as there is no one clear view on how to go forward. However, there are some consistent messages coming out of their words. These messages are presented here, reinforced by the experience gained by the author in quality improvement programmes.

14.3.1 Management support

This point has already been made; however, it is so critical that it can certainly bear repetition. Support of quality improvement (or indeed for any other activity that the company wants to succeed) must start at the very top of the organization.

However, it must also cascade down to middle and junior managers. This requires good communication at the start of any programme. There have been cases where senior managers have involved the shop-floor workers in a quality circle programme for instance, without ensuring full involvement of the supervisory level. This can cause a conflict of interest and pressure being applied to workers who are asked to attend meetings during their working hours and have to justify their absence to their supervisor.

14.3.2 Management commitment

There is a subtle difference between showing support for an activity and being committed to its success. The best way that a senior management team can demonstrate its commitment to quality improvement is to take part in activities themselves. For example, company awareness training on satisfaction of customer requirements should be presented to mixed groups, including board members.

14.3.3 Teamworking

The process of teamworking will be dealt with in much more detail later in the next chapter. At this point it is sufficient to say that the most successful improvement activities are those where people work in teams. These may be from within a single area, as in a quality circle, but are particularly effective when they are cross-functional. They provide an opportunity for people to get together that might normally never meet, let alone work on joint projects. They also allow people to pool knowledge and abilities in order to have sight of 'the bigger picture'.

14.3.4 Asking the right question

It has already been stressed that prevention is better than detection and correction. An increase in prevention costs can result in a drastic reduction in failure costs and also a

lowering of appraisal costs on some occasions. This requires a shift in the way people think about their jobs and the questions they ask.

Instead of asking whether something has been done correctly (appraisal, after the event), it is better to question whether the capability is there to do the job properly. This brings into focus such things as process design, raw material specifications and training of workers.

As an adjunct to this, once it has been determined that customer requirements can be satisfied, the next thing to question should be whether the job is consistently done correctly and whether there are ways of doing it better. This moves the action firmly towards quality improvement.

14.3.5 Breaking out of the silos

In a traditional company, walls tend to build up between different functions within the organization. If not checked, these 'functional silos' can become isolated from one another and see their objectives only in terms of the immediate task of the department. In such cases, there can be suboptimization of performance, since what is best for the performance of one department might not be best for the whole of the company.

A classic example of this is the old-fashioned approach to purchasing of raw materials. When the purchasing department was judged solely on the total budget for purchases and rewarded for buying cheaply, there was no incentive to liaise with the production department on the quality of the material being delivered and the impact that it had on the running of the process machines. However, by breaking out of the silos and considering purchasing as a horizontal process across the organization, with involvement of a number of different functions, a much more effective operation can be achieved.

14.3.6 Acceptance of change

This aspect has two parts to it. First of all, it is important to accept that change is necessary. If people feel that everything is OK and there is no need for improvement, there will be a level of complacency built up, which means that the company will lose its edge with regard to the competition.

There is a view that quality improvement programmes should be established whilst things are going relatively well, since once there are real problems, it is probably too late to do anything about it. However, this can be hindered by the 'if it ain't broke, don't fix it' mentality, which needs to be overcome.

Secondly, change can be very threatening for some people within an organization. They believe that change will make their jobs bigger, harder, less stable or less secure. It is important that the right messages are given in the first place to ensure that people understand that the changes will make their jobs more effective, more value-adding and more stable (assuming that the latter is true, of course).

14.3.7 User driven

A successful quality improvement programme must be user driven if the people within the organization are to take ownership of it and achieve good results. It is not uncommon for companies to use consultants to help introduce the programme, particularly if it is a completely new approach for the company. However, these consultants should be used as facilitators and trainers only: they should advise on how the programme should operate, based on their experience of the tools and techniques. The people working within the company are the experts on their own particular organization and are, therefore, best placed to decide how the tools and techniques can be applied in practice.

There are cases where consultants have been engaged by companies to 'get ISO 9000 accreditation' for them. The consultant has written the quality manual and procedures and presented them to the company. However, without a detailed knowledge of the particular company, it is very difficult to provide a set of documents to which the workforce can commit and of which they can take ownership.

15

Quality tools and techniques

15.1 Introduction

There are a huge number of tools and techniques that can be used within quality improvement programmes. They range from the purely qualitative, like brainstorming and cause and effect diagrams to the statistically based quantitative ones such as Pareto analysis and control charts. In addition, there are completely separate approaches like benchmarking and the application of just in time philosophy.

This chapter does not provide a definitive list; it merely gives an overview of the subject, covering some of the more commonly used ones and some particular favourites of the author. After the introduction of these tools and techniques, there is a more detailed discussion of the human aspects of quality improvement programmes – the issues relating to teamworking.

15.2 Tools for identification of problems

When a team first looks at one or more problems, there needs to be an initial stage of problem identification and definition. This is important, since there is often a tendency to look at symptoms, assume that they are actually causes and hence 'solve' the wrong problem. The first stage is, therefore, to do some creative thinking and measurement in order to differentiate symptoms and causes.

15.2.1 Brainstorming

Brainstorming is a creative method for helping people generate large numbers of ideas in a short space of time. It can be done in a structured way, in which each member of the team offers a suggestion in turn, or as an unstructured session, where everyone shouts out

their ideas as they come to them. In either case, there should be a facilitator who acts as scribe and records all the ideas on a flip-chart.

The basis of brainstorming is to encourage people to think laterally and to come up with ideas that are triggered by what someone else says. It has been shown that a group brainstorming session can generate far more ideas than the same number of individuals working independently.

There are a few rules that must be applied if brainstorming is to be successful:

- the question to be brainstormed is agreed in advance and written on the top of the flip-chart in the form of 'in how many ways could we . . .';
- there should be no criticism or evaluation of ideas during the session;
- freewheeling, i.e. wild ideas, is encouraged;
- the objective should be quantity not quality;
- every idea should be recorded, even repetitions;
- all ideas should be evaluated at the end of the session.

In a successful brainstorming session, more than 100 ideas can be generated by a group of around seven people in 5–10 minutes.

15.2.2 Flow-charting

Flow-charting is a method of displaying the steps in a process pictorially. It is useful for examining how the various steps in a process relate to one another. For example, if a cross-functional team is meeting to review a process that flows horizontally across the organization, it will often be the case that no one member of the team knows the entire process. By using a flow-chart, each member of the team can contribute their knowledge and the whole picture can thus be drawn up.

As a refinement to this, two flow-charts can be drawn: one would present the process as it currently operates; the second would present the ideal situation. By comparing the two, it is possible to highlight problem areas that need further investigation. This process is known as imagineering.

Flow-charts are drawn using symbols for different types of activity within the process. At the simplest level, a rectangle is used to denote a process step, whilst a diamond is used to denote a decision point. It is important that the boundaries of the process are clearly defined from the start.

Figure 15.1 shows a simple flow-chart describing the process of moving from customer enquiry, via purchase order to manufactured and approved product for dispatch.

15.2.3 Check sheets

Check sheets are a sampling technique, which is used to gather information about a particular process in order to see if there are any trends. They are simple forms that can be used to determine how many times a particular event takes place within a certain time period.

There are a few guidelines to be followed in order to ensure that the process is successful. Firstly, it is important that everyone understand exactly what is being

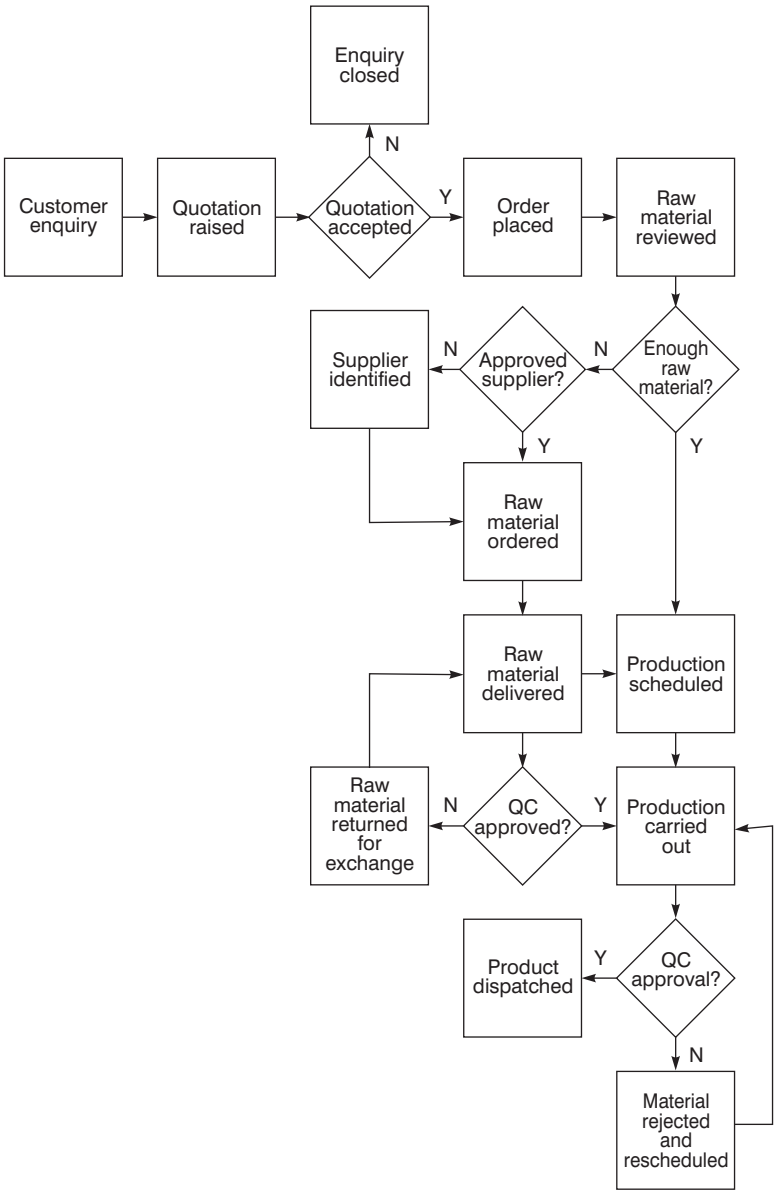

Figure 15.1 A flow-chart for order processing and production.

measured. The observations or samples should be as representative as possible. The sampling process should not be allowed to interfere with the rest of the job, otherwise it will not be done. It is also necessary to ensure that a homogeneous population is being sampled. If this is not the case, then stratification (see later) must be carried out first.

Figure 15.2 shows an example of a check sheet, used to record the reasons why manufacturing records are not approved first time around by the QA department. This

Department	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Warehousing	0	0	0	0	1	0	0	0	0	0	0	0
Manufacturing	2	1	1	0	0	1	3	0	0	1	1	1
Filing	1	1	1	0	1	3	1	0	2	1	1	2
Packaging	8	12	7	19	6	15	11	8	10	14	12	9
QC laboratory	0	0	0	0	0	0	0	0	1	0	0	0

Figure 15.2 An example of a check sheet.

indicates that the packaging department would be a priority area for further investigation.

15.2.4 Stratification

Stratification is used to analyse data, which, although apparently homogeneous, are in fact made up of a number of different classifications of data. Prior to stratification, one conclusion might be drawn but, afterwards, a different set of conclusions can be drawn, and the focus of attention might shift.

Figure 15.3 shows an example of stratification of results from the previous check sheet, stratified for individual supervisors within the packaging department. What looked at first sight like a growing problem across the whole department is now shown to be an improving situation for most of the department, but an obvious area of difficulty for one individual.

Packaging	8	12	7	19	6	15	11	8	10	14	12	9
Team Leader 1	2	3	1	3	1	2	1	0	1	1	0	0
Team Leader 2	1	2	1	3	0	1	2	1	1	0	0	0
Team Leader 3	1	2	1	2	0	1	2	1	1	0	2	1
Team Leader 4	1	1	1	2	1	3	1	1	1	2	1	2
Team Leader 5	3	4	3	9	4	8	6	5	6	11	9	6

Figure 15.3 An example of stratification of results from Figure 15.2.

15.2.5 Nominal group technique

Nominal group technique (NGT) is used to determine priorities amongst a list of problems that a team has identified. It ensures that problems are worked upon that the group as a whole feels to be important. The problems are listed and allocated letters. Each member of the team goes through the list individually and scores the problems according to importance.

For small lists (up to ten items), scoring is used for all items. For example, the most important item in a list of five items is scored as '5', the next is scored as '4' and so on. For longer lists, the 'one half plus one' rule may be applied. For example, in a list

Problem/team member	1	2	3	4	5	Total
A Equipment breakage	2	1	3	3	5	14
B Missing documents	5	4	2	5	4	20
C Due dates missed	3	5	1	4	3	16
D Sampling training	4	3	4	2	2	15
E Laboratory temperature	1	2	5	1	1	10

Figure 15.4 An example of NGT analysis.

of 20 items, the most important item is scored as '11', the next is scored as '10' and so on.

The individual scores are added up and the item with the highest score is the one of most importance to the group as a whole. Figure 15.4 shows an example of an NGT analysis carried out on a list of problems identified by a QC laboratory quality team of five people. It can be seen that 'missing documents' is the most important item, followed by 'due dates missed'.

15.2.6 Pareto chart

A Pareto chart is used to present the relative importance of a list of problems. It is another way to determine which problem should be worked on first. However, unlike NGT, which is a quantification of qualitative views (feelings of individual members of the team), a Pareto chart is based on quantitative data.

The list of problems is compared, using a single set of criteria (such as cost or frequency of occurrence) and the results are presented graphically in decreasing order. An additional

Types of rejects

Underfilled	562	562
Overfilled	190	752
Cracks/pinholes	103	855
Particles	96	951
Mis-shapen tops	49	1000
	1000	

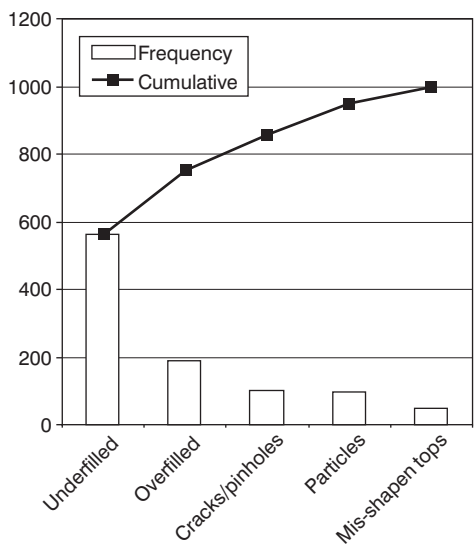

Figure 15.5 An example of a Paeto chart.

refinement would be the addition of a cumulative line to allow the effect of multiple problems to be observed.

Figure 15.5 shows a Pareto chart for a number of different defects that cause filled ampoules to be rejected during inspection. It can be seen that underfilling represents over 50 per cent of the problems and that nearly 80 per cent are due to fill-volume inaccuracies.

15.2.7 Cause and effect diagram

The cause and effect diagram (also known as the Ishikawa or fishbone diagram) is used to display all the possible causes of a chosen problem – the effect. This helps people to get an overview of the full picture, before selecting specific areas to investigate further.

The effect is written in a box on the right-hand side of the page or flip-chart (the head of the fish) and the possible causes are listed on the left. To help clarify the situation, the causes are organized into a number of categories (the structure of the body). The categories that are chosen will depend on the problem being evaluated. In manufacturing, the 4Ms (manpower, machines, methods and materials) are often used. For a service problem, the 4Ps (policies, procedures, people and plant) can be useful.

Causes are generated either by brainstorming or by some kind of pre-construction activities, such as check-sheet sampling. Each cause may then be further broken down if this is found to be useful.

Figure 15.6 shows the start of a brainstorming session on the possible causes for a fall in sales of an OTC cough mixture. The main categories used are the marketing headings of price, promotion, place and product, so far possible causes related to the product itself have been listed.

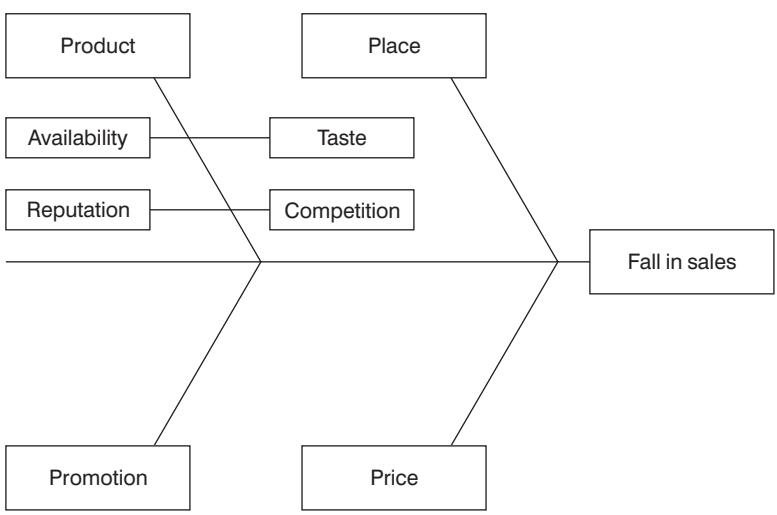

Figure 15.6 An example of a cause and effect diagram.

15.2.8 Run charts

A run chart is a simple graph used to display data. This is a good way of charting progress to see if an improvement is being made. Individual data points are recorded as they are observed. It is important that true trends are recognized, as opposed to simple variations between points.

Figure 15.7 shows a chart of reject levels in batches of tablets compressed over a period of months, during which a number of improvements were made to the machine and its operation.

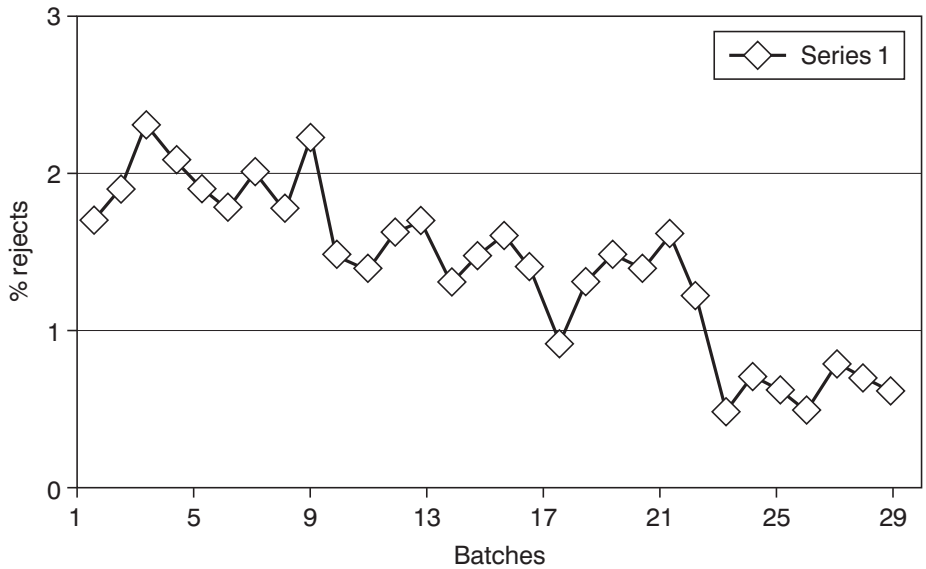

Figure 15.7 An example of a run chart for rejects per batch. Improvements were made between batches 9 and 10, and between 23 and 24. The improvement seen in batch 18 is an anomaly.

15.3 Tools for the analysis of problems

Once the problem has been defined, it will be necessary to analyse the data fully before starting to determine a solution. In many cases, the solution is relatively easy: if the problem is correctly defined, there are often only one or two courses of action that can be taken. The difficulty lies in finding the correct definition in the first place.

Some of the tools discussed in the previous section can also be useful at this stage. In particular, these would be stratification, Pareto charts, cause and effect diagrams, and run charts. However, there are a number of additional tools that can also be used at this stage of the process.

Some of these tools are relatively complex statistical ones. The stages in constructing and interpreting the data require more explanation than is appropriate in this book. What follows below is an overview of each tool only. A statistical reference should be consulted if any of these are going to be used.

15.3.1 Histogram

A histogram is used to display the distribution of results obtained for an individual data measurement in the form of a bar chart. For example, all specifications for packaging materials provide an acceptable range of measurements for each dimension that is specified. It can be useful to know what the spread of results within any one range is likely to be in any given delivery.

The total range of results is divided into appropriate steps, and the number of results falling into each step is then counted. The individual steps are recorded along the *x*-axis of the chart and the number of results within each step is recorded on the *y*-axis.

Figure 15.8 shows the distribution of heights found in a delivery of empty bottles tested by QC. It can be seen that the delivery contains two distinct populations of bottles: although they are all within the permitted range of the specification, it would be likely that use of this delivery could result in problems with the setting of the production machine.

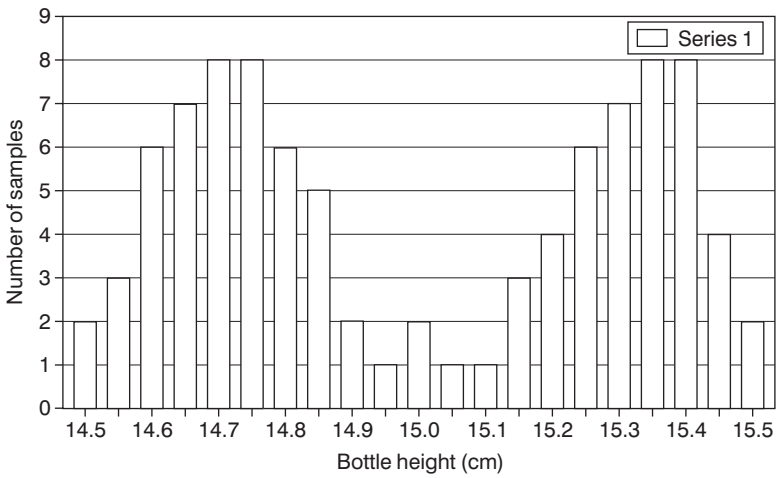

Figure 15.8 An example of a histogram for bottle heights. Standard = 15 cm ± 0.5 cm.

15.3.2 Scatter diagrams

Scatter diagrams are used to examine a suspected relationship between two variables. They cannot prove that changing one variable has an effect on a second variable, but they can demonstrate a relationship between the two.

Of the two variables, the suspected cause is plotted on the *x*-axis and the suspected effect is plotted on the *y*-axis. A suitably large number (50–100) of paired data samples are collected and plotted on the graph. The closer the correlation between the variations in the two, the more likely it is that there will be a relationship.

Figure 15.9 shows an example of two scatter diagrams for the activity of an active ingredient plotted against the length of storage time and outside temperature when the samples were taken. It demonstrates that there is probably a negative correlation between

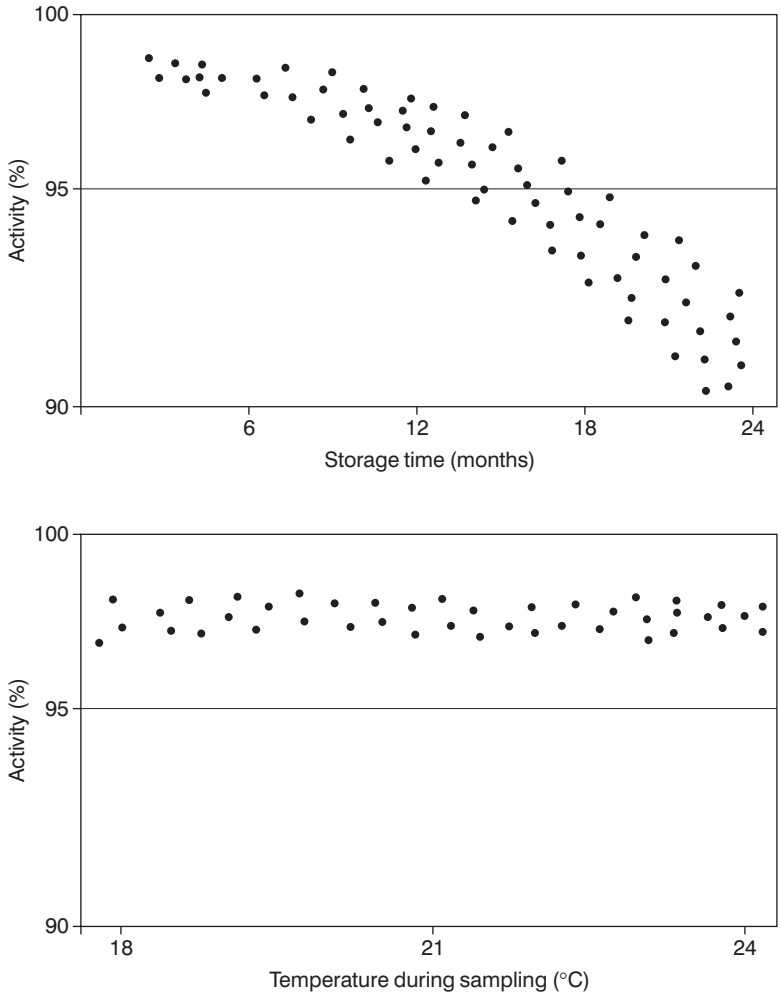

Figure 15.9 An example of two scatter diagrams.

activity and storage time, but a less defined relationship between activity and outside temperature.

15.3.3 Control charts

Control charts are used to display a series of measurements relating to an individual parameter (e.g. tablet weight on a compression machine), in order to determine whether the process is under control in statistical terms. It is a run chart on to which are added lines for the process average, and the upper and lower control limits. In some cases, the control limits are referred to as the action limits and additional alert limits are added within the range.

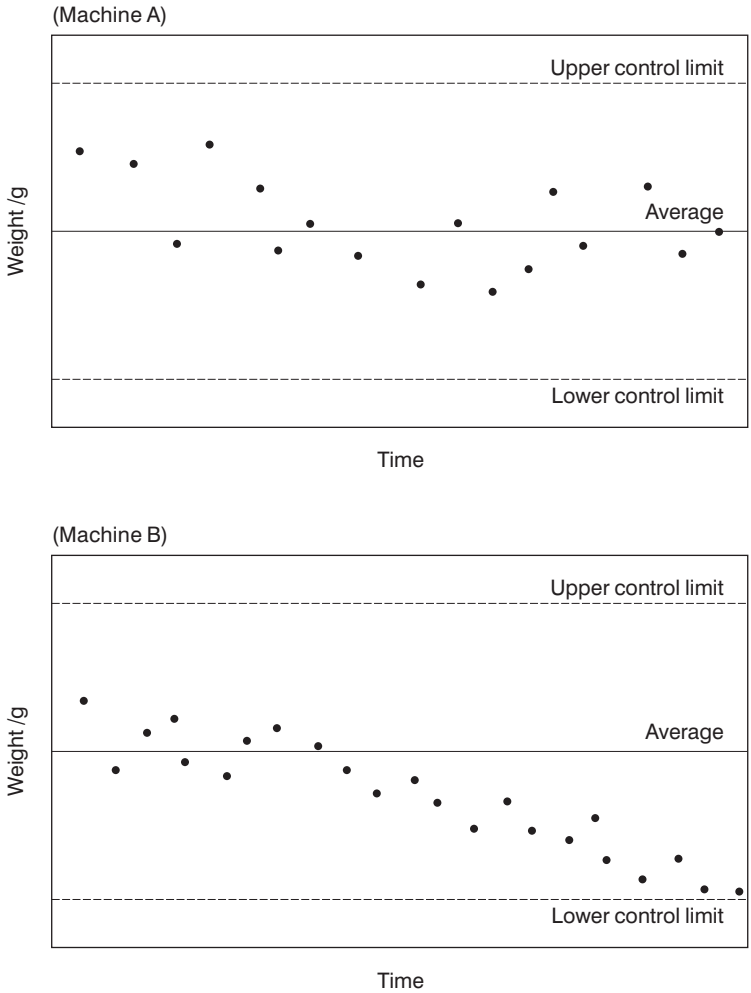

Figure 15.10 An example of two control charts.

Figure 15.10 shows two control charts for the measurement of tablet weight over time during the manufacture of a batch of product using two different machines. It can be seen that despite random variations, the process on machine A is under control, whilst the process on machine B is tending to drift out of control and attention needs to be paid to this particular machine setting.

15.3.4 Process capability

Having shown that a process is in control, it is sometimes necessary to determine whether it can produce product in conformance to the customer's requirements. This can be evaluated by means of process capability. Capability indices are calculated that allow the distribution of the process results to be compared with the limits of the specification.

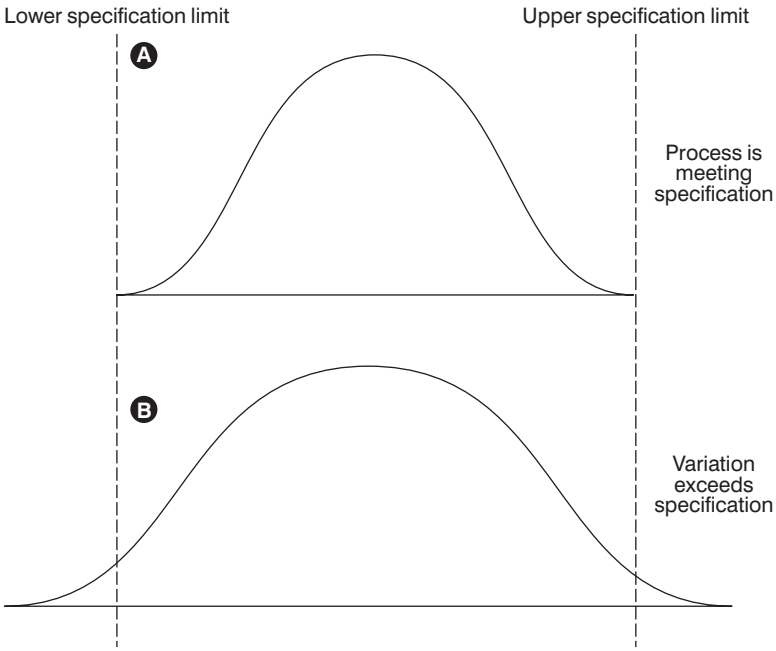

Figure 15.11 Two examples of process capability assessments. A, process is meeting specification; B, variation exceeds specification.

Figure 15.11 shows two examples of process capability assessments for tablet hardness. In example A, all the results are within the control specification limits and the process is capable of conforming to requirements. In example B, some of the results are outside of the limits and some reject tablets would be produced.

15.3.5 Force field analysis

Any quality improvement plan will, by definition, involve an element of change. As was discussed earlier, whilst some people positively welcome change, for others it can be a time of threat or fear. Hence for any change, there are likely to be a series of forces driving it forward and another series of forces restraining it. The examination of these forces was developed by Kurt Lewin into force field analysis.

The entire positive, driving forces are listed on the left-hand side of the page or flip-chart, with arrows pointing to the right; the negative, restraining forces are listed on the right-hand side, with arrows pointing to the left. The line in the centre represents the status quo and the extreme right-hand side represents the required situation. Different lengths of arrow can be used to represent different strengths of force. In order to move from the status quo to the required position, it is necessary either to strengthen the driving forces or (more often) weaken the restraining forces.

Figure 15.12 shows an example of a force field analysis for increasing output on a particular filling line.

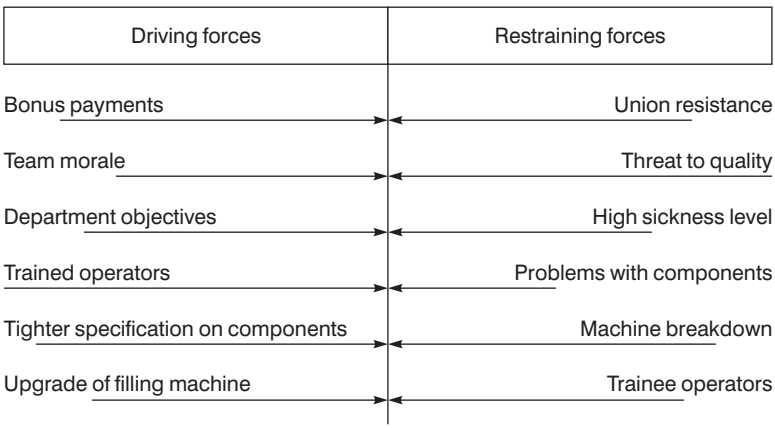

Figure 15.12 An example of a force field analysis.

15.4 Benchmarking

Benchmarking is the practice of being humble enough to admit that someone is better at something and being wise enough to try to learn in order to match or even surpass them at it. Put simply, it is the process of identifying and learning from best practice. It is carried out at the level of a single performance parameter, rather than looking at overall performance. Since individual performance criteria are being examined, it is likely that different members of any study will have examples of best practice for different parameters. Hence all members of the study (which can be anything from two upward) will have something to contribute to the process.

Benchmarking studies have been carried out between different factories within the same group. For example, in a multinational company, the factories in the USA or Western Europe are likely to have the best facilities from a technological point of view and can teach the rest of the group about best practice in production processes, but when it comes to training, the ideas being implemented by companies in Latin America might be far more innovative and could be used throughout the group.

Benchmarking can also be carried out between different companies within the same industry. For example, if a number of pharmaceutical companies carried out a study of manufacturing performance parameters, there would be some that would be able to demonstrate best practice in productivity, whilst others would be better in terms of inventory stock-turn or speed of fulfilling customers' orders.

Finally, benchmarking can be carried out between companies from completely different industries. For example, in a cross-industry study, a mail order catalogue company might be able to demonstrate best practice in the logistics of rapid delivery; a pharmaceutical company might be able to demonstrate best practice in validation of production processes and an internet 'dot.com' company might be able to demonstrate best practice in the use of e-commerce.

There is a vast literature on the subject of benchmarking and a number of institutes and organizations that specialize in facilitation of the process. The two case studies later in this section will illustrate the use of benchmarking in our own industry.

15.4.1 Steps in a benchmarking study

There are a number of models that have been published for carrying out a benchmarking study. In general, they all follow a similar pattern.

Identify parameters and comparators

Benchmarking is carried out against specific parameters. Which ones are chosen to be studied will determine the most appropriate group of candidates for comparison.

Data collection

All members of the study must use the same data collection method, if the comparison is to be a fair one. The method should be agreed in advance and fully understood by all members. An appropriate period of time must be allowed for the data to be collected.

Determination of best practice

Once all the data are collected, the results are reported, best practice can be determined and a gap analysis performed on the results of all the other members. A study can then be made of how the best practice is being achieved.

Setting of goals for improvement

Each member will decide how their performance can be improved, using lessons learnt from the benchmarking study. Action plans are put in place, together with progress monitoring systems.

Doing it again

As performance improves across the group, the level of best practice will hopefully improve (and in fact, the best practice company may change, as members start to leapfrog one another). It is, therefore, useful to repeat the exercise after a time to see whether there are more lessons to be learnt in a process of continual improvements.

15.4.2 Case study 1 – benchmarking in R & D

The senior team of an R & D directorate of a major MNC recognized that, in order to be successful in reducing the time that it took to get a new product to the marketplace, they would have to improve their ability to run projects via a matrix management system. They, therefore, decided to take part in a UK-wide, cross-industry study, involving 14 companies from diverse industries. (There were no other pharmaceutical companies within the study). The companies varied widely in their histories of project management: in terms of experience; there was an engineering consultancy with a long pedigree in project management, and a public service retail organization to which the concept was new.

The R & D team found that they were able to contribute to the study of best practice in understanding risk and moving high-risk projects into development. Unlike many industries, we have no guarantee of a product at the end of the development phase.

The study was carried out in three phases. In phase 1, the scene was set. Data were gathered and used to identify ranges of performance and to position each company with

respect to each parameter. This gave rise to a measurement of each system. In other words, current positions were defined and compared.

In the second phase, the participants homed in on examples of best practice and reviewed their strengths and weaknesses. Ten major performance areas were focused upon.

The third phase was the implementation of best practices and reciprocal site visits. The whole study was based on the belief that all projects have common features and that hence a generic project model could be developed, which would allow analysis of the best use of resources. A number of key performance areas were identified by the study. These are presented in full below, since they could also be applied to the working of teams within a quality improvement programme.

Integrating project work into the organization

It is necessary to reorganize the company along project-based lines, paying attention to management, culture, committees and rewards. In particular, rewards must be geared to project success rather than individual success, whilst at the same time accepting that a failed project may be a success (particularly in this industry).

Managing human factors in projects

Scientists, like many other professionals, do not make particularly good managers – nor are they very easy to manage. With matrix management, where there are in effect two 'bosses' – the functional manager and the project manager – the problem can be compounded. Project management is not recognized by many others as a legitimate profession. The project manager will often only be respected if they can do the functional job better than the professional can.

Defining project 'anatomy'

Any project will have a number of elements within it: risk, time, cost and culture. The skill comes in recognizing the relative importance of each in different projects. For example, in the development of a new drug, risk, time and cost will be the key factors. On the other hand, in a project to computerize a documentation system, the main element may be culture.

Defining and executing projects

Any successful project will have control systems and review systems so that activities can be monitored throughout. A post-project appraisal system is critical for learning the lessons – both good and bad – from one project for application on all subsequent ones.

Estimating cost, time and resource requirements

Construction companies have traditionally been very good at estimating resources, since they operate on such tight margins. Within the pharmaceutical company in the past, cost was not considered to be particularly important and many R & D personnel had no idea of their budgets. This has been gradually changing over the past decade and costs are becoming more important. Time always was and will remain important. In general, a shortage of resources leads to a need for change in thinking, skills and management style.

15.4.3 Case study 2 – benchmarking in manufacturing

The previous case study was an example of functional benchmarking – looking at the same function, carried out in companies across a range of industries. This case study demonstrates the approach of internal benchmarking within a multisite company. The project studied a single process technology, being carried out on a number of sites in different countries. The main aspects that were initially studied were direct and indirect labour (direct filling, direct packaging, production support, QA/QC and technical/engineering support). A second phase was initiated later on, looking at material wastage, in the form of rejects and samples.

The study was carried out using retrospective data, based on simple definitions. For example, for filling, the calculation was the total number of units filled divided into total number of direct operator minutes used to give operator minutes per unit.

From the data, the best in class was identified for each of the parameters being measured. In each case, this factory then analysed itself in order to explain why it was the most successful. Each of the other factories then had the opportunity to comment on this analysis and amend it. The lessons learnt were then applied to all the factories and improvements measured by a continuation of the original measurement.

The first lesson that came out was the need to make sure that the comparison is 'apples and apples', not 'apples and pears'. Although all the factories were working from the same process formulation and with the same equipment, they had had up to 20 years for diversity to creep in. This underlined the importance of clear simple definitions.

It was found to be important to avoid going into too much detail initially; again, this could be controlled by good definitions at the start.

There is also a need to apply sanity checks to the process – and this is where a good facilitator is essential. If any results look too good or too horrendous, it is worth checking that everything is OK before going public with the results. Otherwise, the whole process could be discredited. One of the benefits of such a detailed analysis of a process is that the obvious stupidities can be put right straight away – and there is a chance to get a series of 'quick wins', which is good both for the morale of the group and the credibility of the programme.

One clear message that came out of the exercise is that, as suggested earlier in this section, no one is best of class for all activities. This helped to maintain everyone's confidence in themselves and the process, and ensured that everyone felt they were both contributing to and gaining from the process.

15.5 Using the tools and techniques

Within the context of a quality improvement programme, the tools and techniques are generally used by teams of people working on specific problems or projects. In this section, there is a review of the types of quality team, an overview of a problem-solving model that can be applied to all types of teams and a discussion of the requirements for successful teamworking.

15.5.1 Type of quality teams

There are a number of different types of team that can be set up, depending on the project in hand. They are called by different names within different organizations. The terminology here is taken from Mike Robson of MRA Associates.

The types of teams are differentiated in a number of ways: who makes up the team; who sets the task and, therefore, who has ownership of the task; and who leads the group.

Quality task forces

A quality task force is a cross-functional group, generally set up by a senior manager to examine a specific issue that the manager believes is important enough to be investigated by a dedicated team. Ownership, therefore, sits with the senior manager. The members will generally be made up of people who have knowledge of the task in hand and the group leader will often be a person who has a vested interest in seeing a positive result. The membership will be appointed, rather than made up of volunteers.

Quality department groups

These are similar to quality task forces, except that they will be concerned with a single department and will mainly be made up of members of that department. A few 'outsiders' may be drafted in if they have technical expertise that could provide input to the task. Once again, the task will tend to be set by a senior manager and the team members will be appointed.

Quality circles

These are groups of volunteers who meet together regularly to identify, analyse and solve problems related to their own jobs. As referred to in Chapter 14, quality circles are most widely found in Japan and are associated with the work of Dr Ishikawa. Since the group is completely made up of volunteers, they have complete ownership of the process. The group is often, but not always, chaired by the supervisor of the area. The other main difference between quality circles and other types of quality teams is that they do not just form to look at one problem and then split up. They are ongoing, as part of the continuous improvement programme.

Another major difference between quality circles and the previous types of teams is that responsibility for implementing the improvements generally rests with the team itself. In the earlier groups, it is often necessary for other parts of the organization – and certainly for senior managers – to be involved in implementation of recommendations.

Quality improvement teams

These are similar to quality circles apart from the fact that they cross departmental or functional boundaries. Once again, membership is voluntary. However, they tend to form to look at one specific issue and then disband.

Facilitation

One thing that all the groups have in common is that to be successful, they need to be facilitated. A facilitator is someone who is trained in the process of teamworking and who trains the group in that process. They also act as a trainer in introducing the group to the various problem-solving tools and techniques.

A facilitator does not need to be experienced in the tasks that are being examined. In fact, on many occasions, having a facilitator who does *not* know the technical details is a positive advantage, since it allows for a 'fresh pair of eyes' approach.

15.5.2 Teamworking – the problem-solving approach

Whatever the type of team and whatever the problem that is being tackled, there will generally be a standard set of steps that will need to be carried out.

Definition of the problem

Whether it is a quality circle, starting from a brainstormed list of all the problems that they have or a task force with a set project, it will be critical to define the real problem at the start. It is very easy to confuse causes and symptoms; equally it is easy to fall into the trap of assuming what the problem is. In some groups, the issue of problem definition can take longer to address than the rest of the work; however, if it is done successfully, it greatly increases the probability of finding an effective solution.

Analysis and data collection

Starting with a well-defined problem, the next stage would be to analyse the possible causes and then to collect hard data to support the analysis.

Interpretation of data and definition of the solution

After collecting the data, they are presented to the group in an effective manner (the more pictorially, the better) and used as the basis for generating possible solutions. From all the possible solutions (and there may often be only one or two options), the best solution in the view of the team is chosen.

Approval of recommendations

In most cases, the team will need to obtain approval for any given solution, even if they are going to be responsible for implementation. This is best done by a communication exercise, such as a presentation to the senior team. This can also be used as an opportunity to publicize the activities of the group and thereby increase the credibility of the overall programme.

Implementation and monitoring

Unless the solution is implemented, the team will have wasted their time. Unless performance is monitored, there will be no way of knowing whether implementation has been successful or not. Hence there needs to be an ongoing exercise of data collection, albeit not necessarily at the same level of intensity as in the earlier stages.

15.5.3 Teamworking – the process skills

To carry out the tasks that the team has been given (or has chosen for themselves), it is necessary to use a structured problem-solving approach as detailed above. The use of tools and techniques is also required.

However, there is a third aspect of teamworking – that of the process skills required to operate effectively. As referred to above, this is best accomplished via a facilitator. However, it is also worth the team knowing something about group dynamics and what makes a team work most effectively and efficiently.

Setting aims

Aim setting is an important part of effective teamworking. It is the process that helps people visualize what they want to achieve in the future. In the context of a problem-solving team, this will come at the stage of problem definition. There is a need to define a purpose to the activity, the end result that should come out of the work and the success criteria by which the effectiveness can be judged. Figure 15.13 shows an example of an aim statement for a quality team investigating a delay in the approval of batches of finished product.

Project team aim statement

> Our aim is to identify and quantify the main reasons for delays in the approval of batches of Product X and to propose measures for reducing the approval period by 50% within three months of commencement of the investigation.

Figure 15.13 An example of a project team aim statement.

Preparing for action

Rather than diving straight into the task, it is important that the team prepares effectively. The team needs to identify what information is already known and what needs to be obtained. There should also be a well-defined plan of action, which defines *who* will do *what, where* they will do it, *when* they will do it and *how* it will be done.

Action

After all the preparation, people must be committed to carrying out their roles within the team effectively, so that the plan can be carried out to schedule.

Review

It is always possible to learn from experience. As well as monitoring the solutions that are implemented to ensure that they are successful, there is also much to be gained by reviewing how the team has operated from a process point of view. It can be difficult for members to do this, as it requires an open, supportive atmosphere and the trust required to both give and receive feedback. However, it can be a very worthwhile experience, if carried out successfully.

15.6 Summary

This chapter builds on the previous one and reviews the practical aspects of using tools and techniques in the context of a quality improvement programme. It introduces a range

of methodologies; however, for most of them, a more detailed explanation should be sought, together with appropriate training, if they are to be used successfully.

The tools and techniques are used most effectively by groups of people working together as teams. Teamworking has been discussed both from the viewpoint of the problem-solving approach and from the point of view of the process of working in teams. The latter subject in particular has resulted in a large amount of research and literature, and a few appropriate references are given in the Bibliography.

16

World class manufacturing in the pharmaceutical industry

16.1 Introduction

World class manufacturing is the continual and rapid improvement in all areas of manufacturing. Alternatively, it is the principle of total quality management applied to the manufacturing environment. This final chapter takes the material covered in the previous two chapters and converts it into practical experience within the pharmaceutical industry.

For most businesses at the start of the twenty-first century, particularly those in the developed world, good quality and a reasonable price are taken for granted. They may be considered as order qualifiers or the entry requirements for the race to the customers. For order winners, it is necessary to look elsewhere. Consideration should be given to the product design, the order process, customer lead times, reliability of delivery, after sales support and the invoice process. Even companies within emerging industries are learning these lessons rapidly in the attempt to compete in the global marketplace.

It is important, however, to ensure that a move towards world class manufacturing leads to an improvement in the overall performance in the company if a competitive advantage is to be obtained. Functional excellence alone can lead to isolation and reduction in overall company performance. The true aim must be for business excellence and hence the first lesson that must be learnt by manufacturing personnel is the development of teamwork with colleagues in other parts of the organization.

16.1.1 A return to benchmarking

There are a number of key parameters relating to manufacturing that can be used to benchmark an organization against world class performance. These are shown in Table 16.1, together with some typical data, where available, for pharmaceutical companies in the UK.

Table 16.1 Benchmarking in the pharmaceutical industry

Performance parameter	WCM	UK best	UK average	UK worst
Annual inventory turns (RM and WIP only)	100	15.2	4.5	1.9
Production quality problems (rejects per million – WIP only)	200	0.1%	4%	15%
Customer service	99%	99%	88%	68%
Product cost (compared to multinational competition)	—10%			
Average changeover time (good part to good part)	<5 minutes	30 minutes	6 hours	24 hours
Production batch size (total usage expressed in days)	<1			
Utilized capacity (as % of total shift capacity)	95%	100%	60%	20%
Value added time (as % of total production lead time)	>50%			

Source: Various, personal experience.

16.1.2 Are pharmaceuticals different?

Whenever the topic of world class manufacture or benchmarking is raised in relation to the pharmaceutical industry, people tend to say 'Ah, but we are different; that won't work in our industry'.

Whilst it is true that pharmaceutical manufacture has some very specific requirements relating to quality of product and production environment, the concepts that relate to world class manufacture are applicable to all industries and it is the basic concepts that should be considered rather than the absolute values quoted for a particular parameter. Additionally, it should be remembered that many of the examples of best practice are found in the electronics industry, which also has high-quality standards for manufacture, but which is in an even more competitive market than is pharmaceuticals.

16.2 Areas for improvement

16.2.1 Set up and changeover times

This is particularly relevent to packaging lines. As machines increase in the degree of complexity, the time taken to carry out changeovers between different products increases. As machine speeds increase and market requirements become more refined, the length of time taken to complete any given packing run reduces. Hence the balance between productive and non-productive time shifts gradually in the wrong direction. Significant savings can be made by detailed analysis of all the activities involved in the changeover to determine where time savings can be made.

Case study

The team running a blister packaging line for tablets were averaging a changeover time of six hours. They were given the target of cutting the time by 50 per cent. Since they had

already been running an improvement programme on the line, they realized that a step-change would be needed if they were to achieve their target.

Following a full study of the line, involving data collection and analysis, taking a video of the changeover process and visits to other factories to collect ideas, a number of areas were identified where improvements could be made:

- Modifications were made to the line in a number of areas, to increase the speed of changeover and reduce the cleaning tasks required.
- Scheduling of the line was investigated and reorganized such that the number of changeovers was minimized.
- Packaging components were rationalized in terms of size, such that a product changeover did not necessarily mean a change to the machine parts.
- The changeover process was proceduralized in the same way as production, so that all personnel carried out tasks in the same order and in the same way.
- Activities that were previously carried out serially were organized in parallel.
- Activities that could be done in advance were moved off line.
- The changeover was carried out in phases, by splitting the line into sections and beginning as soon as work on the previous batch was completed in that part of the line.

As a result of introducing the changes listed above, the team exceeded their target and reduced the average changeover time by 51 per cent.

16.2.2 Product flow philosophy

One of the factors that reduces effectiveness in manufacturing operations is the downtime and double-handling that takes place between stages of manufacture. For example, the storage of granules prior to compression or compressed tablets prior to packaging. Whilst the continuous production lines seen in the highly-automated automobile industry are an extreme example, the product flow philosophy that they demonstrate is one that should be aspired to in world class manufacturing. The more processes that can be run in an integrated way, the less downtime and double-handling.

16.2.3 Flexibility of skills

This is a topic that has to be treated with caution. Its application and effectiveness within a company will depend on such factors as trade union strength, labour legislation, and local custom and practice.

In general terms, the more demarcation that exists on a factory floor, the more opportunity there is for downtime. If the mechanic that is due to carry out a machine changeover has been called away to deal with a breakdown on another line, or if the mechanic mending a pump has to call an electrician to carry out a simple rewiring task, every delay will reduce the productivity of the line. Obviously a skilled tradesperson has core skills that cannot be carried out by untrained personnel. However, there may be tasks at the periphery of each role that could be carried out by a variety of different people. If

this can be formalized, the nearest available person, suitably-trained, can continue with the activity when it is required.

Case study

In a plant producing pharmaceutical actives, it was traditionally the role of the mechanical engineer to strip down and clean filters on the process lines. In a time of high productivity, the engineering resources tended to be working on maintenance or repair work. They were thus unable to keep up with the number of changeovers and the process operators (and the plant) were left idle waiting for an engineer to become free.

After discussion with both parties, it was agreed that the process operators should be trained in the non-engineering aspects of the changoever, including changing the filters. As a result, downtime was reduced significantly and productivity increased.

16.2.4 Involving suppliers in the business

Traditionally, the relationship between manufacturers and their suppliers has been an adversarial one. The manufacturer as customer wanted as much as possible, as quickly as possible, for as little as possible. The supplier would look for opportunities to increase the price.

The more appropriate relationship within a world class manufacturing company is one of partnership with the supplier. It should be based on a win–win situation in that parties should understand what the other requires from the relationship. It may be that the supplier is required to make an investment in order to improve the quality of the product or provide a competitive advantage to the manufacturer. For this to happen, there will need to be some kind of commitment from the manufacturer that the business will remain for a specified period of time.

The advantage to the supplier is a guaranteed order book; the advantage to the manufacturer is a guaranteed supply at acceptable quality levels. This may enable the number of approved suppliers to be reduced, with a subsequent reduction in QA testing, supplier audits and stock holding costs.

Case study

A production department involved in tablet packaging was using statistical process control techniques to monitor the quality of output. They identified that there was a problem with the cartons supplied to the automatic cartonning machine. The specification for the component gave 11 separate parameters that were monitored by QC on delivery. No recent batches had failed to comply with the specification.

On discussing the problem with the supplier, it transpired that of the 11 parameters measured, only three were subject to any variation during manufacture. Hence eight of the tests were meaningless. On the other hand, a major variable in the carton manufacturing process, which had a significant effect on the performance of the cartonning machine was totally ignored by the specification and hence had not been controlled by the supplier. Once the specification had been amended, the quality of the carton improved and the problem went away.

Had the specification been drafted in conjunction with the supplier, who after all was the expert on manufacture of cartons, the situation could have been avoided in the first

place. As a result of the better understanding between the two companies, all future specifications were prepared jointly and production problems thus minimized.

16.2.5 Reducing variability at all stages

In a time when customer requirements are paramount and a flexibility of approach to pack, print, etc. is important, it may seem paradoxical to suggest that variability should be reduced. However, the trick is to reconcile these two apparent contradictions. The best example of this is to be found in the automobile industry where the degree of choice (colours, fabrics, etc.) provided to the customer results in each car being apparently custom-made, whilst still being assembled on the automated production line.

Some areas where variability can be reduced are as follows: materials, components, suppliers, machines and rejects. Each of these will be addressed in turn.

Materials

At the development stage, given the choice between using, for example, as an excipient in a tablet, a material that is already in use within other products in the portfolio, and a material that is new to the company, it is preferable to opt for the former. (The assumption here is that there is no scientific or clinical reason to choose one over the other.) Use of the familiar material prevents potential increases in the number of suppliers and supplier audits, the number of stock keeping units, the number of specifications that need to be developed and the number of quality control tests that have to be carried out.

Components

On a packaging line there are a number of components involved in the finished pack. For example, for a liquids filling line, there is the bottle, the cap, the bottle label, the instruction leaflet, the spoon, the carton and the shipping outer. If different products carry different specifications and dimensions for these components, the number of variables builds up significantly.

From the point of view of the customer, these differences are irrelevant. It is unlikely that a customer complaint has ever been generated by the size of a cap. Product differentiation comes from the print on the carton and label, not from their dimensions. Often, the differences are a matter of history rather than logic. Elimination of these differences can be very cost-effective, without impacting on the customer in any way.

A tablet packaging line was found to have over 50 different components in use for the range of products packed. By streamlining the size of cap, the shape and size of the label, and the size of the instruction leaflet, the number of components was reduced to 26, thus cutting drastically the number of machine changeovers that were required.

Suppliers

The point has already been discussed above, regarding the importance of developing a good relationship with suppliers. Each supplier that is used requires a supplier audit to be carried out, taking up the time of QA, production and purchasing personnel. If there is only one approved source for a material or if several different materials are sourced from the same supplier, the resources required for these activities are reduced.

Machines

Many factories are equipped over time. The asset register gradually grows as business demand increases and more capacity is required. Hence it is common to find machinery of different ages located together in one plant. Frequently, these will be different types, from different suppliers, depending on the preference of the particular purchaser and the price deals on offer at the time of purchase.

One of the key criteria that should be assessed when making a purchasing decision is 'what do we currently have'. Assuming that the current machinery has performed satisfactorily, there will be an investment already made in terms of operational and maintenance experience, together with relationship with the company. The benefit of this investment should be balanced carefully against the perceived benefits of any alternative supplier.

Process

A detailed examination of process variability can bring about amazing results on occasion. A quality team within an ampoule-filling area found that there was a significant overage being filled into each dose of a particular product. Subsequent investigation revealed that the filling limits had been set by QC when the product was first launched many years ago, in order to ensure that the specified dose could always be obtained from each unit. Over time, the accuracy of the filling pumps had greatly improved, but the overage had never been reduced. It was possible to reduce the overage without affecting the quality of the product in any way and consequently increase the yield on each batch of that product by 16 per cent.

Rejects

Over the years, the measure for 'acceptable' reject level has gradually decreased. In the 1980s, the West was still talking in terms of percentage points of rejects. At the same time, talk in Japan was of 'parts per million'. The goal that we should all be aiming for is 'parts per billion'.

Reduction in leadtimes

Leadtime in manufacturing terms can be measured from the point that material starts to be processed to the day that the finished product becomes available for sale. All the time that the product cannot be released for sale, it is incurring costs as inventory. Every effort should be made to reduce leadtimes to a minimum.

A quality circle in a tablet manufacturing plant was asked to investigate why the leadtime on approval of product was growing rather than reducing. They found that the main problem related to a particular document, a process deviation form, that was raised in cases where any non-standard activity had taken place during production. Once a process deviation had entered the system, it could add up to three weeks to the leadtime for that batch of product. On tracing the route of the process deviation form, they found that it was passing the desks of 11 different people in four different departments across the site.

Further examination revealed that of the 11 people, only three were involved in the approval process. The remaining eight were seeing the document for information purposes only. Some of them did not realize that they were holding up the system by not processing the document as soon as it appeared. After discussion, the system was changed such that

the original document went to three people only, the remainder receiving a copy for information only. The system speeded up considerably and leadtimes fell again.

16.2.6 Getting rid of bad habits

One of the problems that is seen on occasion in a manufacturing process is a build-up of process drift, in that changes in procedure occur. If they are not corrected, they become part of the accepted procedure from then on. If they are adverse to the product, then it is likely that they will be corrected as soon as they occur. The situation is not so clear cut when the changes are introduced for the good of the product. The case study below discusses this issue and also covers a number of other aspects reviewed earlier in this section.

Case study

A quality team was set up to investigate leadtimes and sampling of a new product line in the biotechnology department. The leadtime was increasing and the costs associated with sampling were spiralling. On investigation, a number of issues were found:

- The tests for which the samples were being taken were partly regulatory ones, and partly those requested by QC or development for a variety of reasons.
- The extra samples had often been requested as a result of a one-off incident during production, but the request had not been countermanded and the samples kept being taken.
- The samples were being sent to a variety of different locations and non-standard documentation was being used.
- The results were not always being returned on time, to the right person, in the right format.

A thorough review of all samples was made and any non-essential ones removed from the system. Any future non-standard samples had to be raised using a 'temporary request form', which was reviewed on a three-monthly basis and only renewed if the need for the extra samples was still there. A standardized system of documentation was set up for all samples, irrespective of where they were being tested. This included a set route and timescale for the return of results.

As a result of these measures, there was an immediate 41 per cent reduction in the cost of samples and testing – at a value of £350 000 per annum. In addition, the leadtime on the product was reduced significantly.

16.3 Summary

Continuous improvement is rarely brought about by single large steps, because problems are rarely due to a single cause. In each of the case studies quoted above, there have been many small improvements – often brought about very cheaply or at no cost at all. It is all those small improvements that combine to bring about a great result.

It is worth concluding this chapter with the words of Jan Carlzon, CEO of SAS Airlines: 'We did not do one thing 1000% better – we did 1000 things 1% better'.

Glossary

Definitions are taken from a variety of published documents referenced in the bibliography, with additions by the author where appropriate.

batch A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.
blinding (in the context of clinical trials) The process by which one or both parties to a clinical trial is unaware of whether the drug or a placebo is administered to a particular subject.
bulk product Any product which 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 a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.
change control A process by which any change is identified, justified and approved before being carried out.
clean area/clean room 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.
comparator product (in the context of clinical trials) An investigational or marketed product (i.e. an active control) or placebo used as a reference in a clinical trial.
contra-indications Situations in which it is inadvisable or unsafe for a patient to take a particular pharmaceutical.
cross contamination Contamination of a starting material or of a product with another material or product.
excipient A material, other than the active ingredient, added to a pharmaceutical product for the purposes of bulking, preservation or process requirements.

fill-volume The amount of product dispensed into a single primary container at the filling machine.
finished product A medicinal product that has undergone all stages of production, including packaging in its final container.
good manufacturing practice That part of QA, 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.
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 specification. The control of the environment or equipment may also be regarded as a part of in-process control.
intermediate product Partly processed material that must undergo further manufacturing steps before it becomes a bulk product.
in vitro Studies that are carried out in an artificial environment, such as a test-tube, rather than inside a living organism.
in vivo Studies that are carried out inside a living organism.
inspection (in the context of QC) The physical examination of a sample of material to determine whether it complies with the required specification.
manufacture All operations of purchase of materials and products, production, quality control, release, storage, distribution of medicinal products and the related controls.
medicinal products Any medicine or similar product intended for human use, which is subject to control under health legislation in the manufacturing or importing state.
over the counter medicines Medicines that may be purchased without a prescription and without the supervision of a pharmacist.
pharmacovigilance The surveillance of the safety of a medicinal product during its life on the market.
placebo A finished product containing no active ingredient.
primary container/packaging material The container that a pharmaceutical is packed into, and that comes directly into contact with the product. For example, an ampoule, blister film/foil pack or a glass bottle.
production All operations involved in the preparation of a medicinal product, from receipt of materials, through processing and packaging, to its completion as a finished product.
product security The process of ensuring that complete separation is maintained between different batches of the same material or product, or between different materials or products.
public service obligation The obligation placed on wholesalers to guarantee permanently an adequate range of medicinal products to meet the requirements of a specific geographical area and to deliver the supplies requested within a very short time over the whole of the area in question.
qualification Action of proving that any equipment works correctly and actually leads to the expected results. The term 'validation' is sometimes widened to incorporate the concept of qualification.
quality assurance A wide-ranging concept that covers all matters which individually or collectively influence the quality of a product.
quality control That part of GMP that is concerned with sampling, specifications, 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.

secondary packaging material The outer packaging that covers a primary container and does not come directly into contact with the product. For example, individual cartons for blisters or bottles, outer cartons for multiple packs.

starting material Any material (either active material or excipient) used in the production of a medicinal product, excluding packaging materials.

stock keeping unit (SKU) The distinct pack sizes in which a product is sold. Each size would constitute a separate SKU in a wholesaler's catalogue.

testing (in the context of QC) The chemical or microbiological examination of a sample of material to determine whether it complies with the required specification.

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

wholesale distribution (of medicinal products) All activities consisting of procuring, holding, supplying or exporting medicinal products, apart from supplying medicinal products to the public.

Bibliography

Arab Union of the Manufacturers of Pharmaceuticals and Medical Appliances (AUPAM) (1995) *Arab Guidelines on Good Manufacturing Practices for Pharmaceutical Products GMP.*

British Standard 5295, 1989 *Environmental Cleanliness in Enclosed Spaces*.

British Standard BS EN 30012–1:1994 *Meteorological Confirmation System for Measuring Equipment.*

BS 6143–1:1992 *Guide to the Economics of Quality. Process Cost Model.*

BS 6143–2: 1990 *Guide to the Economics of Quality. Prevention, Appraisal and Failure Model.*

Code of Federal Regulations Title 21 Food and Drugs, *Part 211–Current Good Manufacturing Practice For Finished Pharmaceuticals.*

Code of Federal Regulations Title 21 Food and Drugs, *Part 210–Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General*.

Commission of the European Communities (ed.) (1992) *The Rules Governing Medical Products in the EC. Vol IV. Good Manufacturing Practice for Medicinal Products*. Office for Official Publications of the EC, Luxembourg.

Commission of the European Union (ed.) (2000) *Pharmaceuticals in the European Union.* Office for Official Publications of the European Communities, Luxembourg.

Committee for Proprietary Medicinal Products, CPMP/QWP/054/98 (1998) *Annex to Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96): Decision Trees for Selection of Sterilisation Methods*.

Committee for Proprietary Medicinal Products, CPMP/QWP/158/01 (2001) *Note for Guidance on Quality of Water for Pharmaceutical Use*.

Cope, M. (2000) Analytical method validation. *European Journal of Parenteral Sciences* **5**(4), 93–96.

Council Directive 65/65/EEC *on the Approximation of Provisions Laid Down by Law, Regulation or Administrative Action Relating to Medicinal Products*.

Council Directive 75/318/EEC *on the Approximation of the Laws of Member States Relating to Analytical, Pharmatoxicological and Clinical Standards and Protocols in Respect of the Testing of Medicinal Products.*

Council Directive 80/778/EEC *Relating to the Quality of Water Intended for Human Consumption.*

Council Directive 91/356/EEC *Laying Down the Principles and Guidelines of Good Manufacturing Practice for Medicinal Products for Human Use.*

Council Directive 92/27/EEC *on the Labelling of Medicinal Products for Human Use and for Package Leaflets.*

Council Directive 92/28/EEC *on the Advertising of Medicinal Products for Human Use.*

Council Directive 95/319/EEC *on the Approximation of Provisions Laid Down by Law, Regulation or Administrative Action Relating to Medicinal Products.*

Council Regulation (EEC) No 2309/93 of 22 July 1993 *Laying Down Community Procedures for the Authorization and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Agency for the Evaluation of Medicinal Products.*

Crown Copyright 1999 *The Good Laboratory Practice Regulations.* The Stationery Office Limited, London.

Crown Copyright 2000 *The Supply of Unlicensed Relevant Medicinal Products for Individual Patients*. MCA Guidance Note No 14. MCA, London.

Dale, B. and Plunkett, J. (1989) *The Case for Costing Quality.* Department of Trade and Industry, London.

Davies, P. (2001) Harmonising the training of qualified persons in Europe. *European Journal of Parenteral Sciences* **6**(2), 43–46.

Department of Community Services and Health (ed.) (1991) *Australian Code of Good Manufacturing Practice for Therapeutic Goods.* J S McMillan Printing Group, Commonwealth of Australia.

Directive 2001/20/EC of the European Parliament and of the Council *on the Approximation of the Laws, Regulation and Administrative Provisions of the Member States Relating to the Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use.*

EN/ISO 14644-1 1999 *Cleanrooms and Associated Controlled Environments, Classification of Air Cleanliness.*

EN/ISO 14644-2 2000 *Cleanrooms and associated controlled environments. Specifications for testing and monitoring to prove continued compliance with ISO 14644-1.*

EN/ISO 14644-4 2001 *Cleanrooms and associated controlled environments. Design, construction and start-up.*

EN/ISO 14644-7 (draft) *Cleanrooms and associated controlled environments. Separative enclosures.*

EN/ISO 14644-5 (draft) *Cleanrooms and associated controlled environments. Operations.*

EN/ISO 14644-3 (planned) *Cleanrooms and associated controlled environments. Metrology and test methods.*

EN/ISO 14644-6 (planned) *Cleanrooms and associated controlled environments. Terminology.*

EN/ISO 14644-8 (planned) *Cleanrooms and associated controlled environments. Molecular contamination.*

European Commission 94/C63/03 Guidance document 1994: *Good Distribution Practice of Medicinal Products for Human Use.*

European Communities Council Directive (1975) 75/319/EEC (the Pharmaceutical Directive) as amended by Directives 85/570/EEC and 93/39/EEC (Human medicines).

European Communities Council Directive (1992) 92/25/EEC *The Wholesale Distribution of Medicinal Products for Human Use.*

Goldberger, F. (1991) *Pharmaceutical Manufacturing* Ebur 2–9506062–0-2.

ICH Guideline (Q2A) (1994) *Text on Validation of Analytical Procedures*.

ICH Guideline (Q2B) (1996) *Validation of Analytical Procedures: Methodology.*

ISO 8402 (1994) *Quality Vocabulary – International Terms.*

ISO 9000–1 (1994) *Quality Management and Quality Assurance Standards – Part 1: Guidelines for Selection and Use.*

ISO 9000–2 (1993) *Quality Management and Quality Assurance Standards – Part 2: Generic Guidelines of the Application of ISO 9001, ISO 9002 and ISO 9003.*

ISO 9000–3 (1991) *Quality Management and Quality Assurance Standards – Part 3: Guidelines of the Application of ISO 9001 to the Development, Supply and Maintenance of Software.*

ISO 9001 (1994) *Quality Systems – Model for Quality Assurance in Design, Development, Production, Installation and Servicing.*

ISO 9002 (1994) *Quality Systems – Model for Quality Assurance in Production, Installation and Servicing*.

ISO 9003 (1994) *Quality Systems – Model for Quality Assurance in Final Inspection and Test.*

ISO 10011–1 (1990) *Guidelines for Auditing Quality Systems – Part 1: Auditing*.

ISO 10011–2 (1991) *Guidelines for Auditing Quality Systems – Part 2: Qualification Criteria for Quality System Auditors.*

ISO 10011–3 (1991) *Guidelines for Auditing Quality Systems – Part 3: Management of Audit Programmes.*

ISO 10012–1 (1992) *Quality Assurance Requirements for Measuring Equipment – Part 1: Metrology Confirmation System for Measuring Equipment.*

ISO 10013 (1995) *Guidelines For Developing Quality Manuals*.

ISPE Baseline Pharmaceutical Engineering (2001) *Volume 4, Water and Steam Systems.*

Malchi, G. and McGurk, H. (2001) Increasing value through the measurement of the cost of quality (COQ) – a practical approach. *Pharmaceutical Engineering* **21**-3, 92–96.

Medicines Control Agency (ed.) (1977) *Rules and Guidance for Pharmaceutical Manufacturers and Distributors.* The Stationery Office, London.

Mittelman, M. W. (1986) Biological fouling of purified water systems: Part III Treatment. *Microcontamination*, January 1986.

Organization of Pharmaceutical Producers of India (1996) *Quality Assurance Guide.* 3rd revised edition.

Parenteral Society Technical Practice Monograph No 2 (1989) *Environmental Contamination Control Practice.*

Pharmaceutical Inspection Convention/Pharmaceutical Inspection Co-operation Scheme PI 002–1 *Recommendations of Quality System Requirements for Pharmaceutical Inspectorates.*

The Evolution of US Drug Law on the FDA website (http://www.fda.gov/fdac/special/newdrug/benlaw.html).

The Institute of Biology, The Royal Pharmaceutical Society of Great Britain, The Royal Society of Chemistry (1993) *Code of Practice for Qualified Persons.* Register of Qualified Persons. London.

The Medicines (Standard Provisions for Licences and Certificates) Regulations (1971). *Standard Provisions for Wholesale Dealer's Licences*.

UK Government (1971) Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 (SI 1971 No 972) as amended by Amendment Regulations 1972 (SI 1972 No 1226), 1977 (SI 1977 No 1053), 1983 (SI 1983 No 1730), 1992 (SI 1992 No 2846) and 1993 (SI 1993 No 833).

US Federal Standard 209D (1988) *Cleanroom and Work Station Requirements, Controlled Environments.* Institute of Environmental Sciences and Technology.

US Federal Standard 209E (1992) *Cleanroom and Work Station Requirements, Controlled Environments.* Institute of Environmental Sciences and Technology.

US Food and Drug Administration (1983) *Guide to Inspection of Computerized Systems in Drug Processing*.

US Food and Drug Administration (1987) *Guidance on Sterile Drug Products Produced by Aseptic Processing*.

US Food and Drug Administration (1993) *Guide to Inspections of High Purity Water Systems.*

US Food and Drug Administration (1999) *Guide to International Inspections and Travel.*

US Food and Drug Administration (2001) *Investigations Operations Manual*.

USA Environmental Protection Agency 40 CFR, Parts 141 and 142 *National Primary Drinking Water Regulations.*

Wood, J., Hirayama, J. and Satoh, S. (2000) Hot water sanitization of continuous electrodeionization systems. *Pharmaceutical Engineering*, **20**–6, 34–40.

World Health Organization (1969} Quality control of drugs. In: *Twenty-second WHO Health Assembly, Boston, Massachusetts, 8–25 July 1969. Part 1: Resolutions and Decisions, Annexes.* WHO, Geneva.

World Health Organization (1975) Certification scheme on the quality of pharmaceutical products moving in international commerce. In: *Twenty-eighth World Health Assembly, Geneva,* 13–30 *May 1975. Part 1: Resolutions and Decisions, Annexes.* WHO, Geneva.

World Health Organization (1988) WHO Certification scheme on the quality of pharmaceutical products moving in international commerce. In: *Forty-first World Health Assembly, Geneva 2–13 May 1998. Resolutions and Decisions, Annexes*. WHO, Geneva.

World Health Organization (1992) WHO Expert Committee on Specifications for Pharmaceutical Preparations, 32nd report, *Good Manufacturing Practices for Pharmaceutical Products.* WHO, Geneva.

World Health Organization (1992) Annex 2, Provisional guidelines on the inspection of pharmaceutical manufacturers. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, 32nd report. WHO, Geneva.

World Health Organization (1996) Annex 10, Guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, 34th report. WHO, Geneva.

Useful websites

EU Pharmaceuticals and Cosmetics Unit: http://pharmacos.eudra.org
European Commission's EUROPA server: http://europa.eu.int
European Medicines Evaluation Agency (EMEA): www.emea.eu.int
Food and Drug Administration (FDA): www.fda.gov
FDA inspection manuals: www.fda.gov/ora/inspect_ref/default.htm
International Conference on Harmonisation (ICH): www.ich.org
International Organization for Standardization (ISO): www.iso.ch
Pharmaceutical Inspection Co-operation Scheme (PIC/S): www.picscheme.org
Royal Society of Chemistry (RSC): www.rsc.org
World Health Organization (WHO): www.who.int

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