How to Set Up and Manage Quality Control and Quality Assurance

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Summary

This document provides a general introduction to clarify the differences between quality control (QC) and quality assurance (QA). In addition it serves as a starting point for implementing a quality system approach within an organization. The paper offers practical guidance to the implementation of quality and the importance of QC in its relationship to QA. It can be used in conjunction with the various quality regulations or guidelines. Appendix A provides a table of examples of various activities, which will help guide the user to apply a quality system with both QC and QA aspects. It is important to note, however, that the items listed in the table are only examples and should not be regarded as the only way to set up a QC/QA system. Appendix A is based on the Good Laboratory Practice (GLP) quality system. In conclusion, QC is part of effective project management while QA assesses the effectiveness of the quality systems associated with the overall process. Copyright © 2005 John Wiley & Sons, Ltd.

Key Words: good laboratory practice; GLP; project management; quality assurance; quality control; quality management

Aim

This document may be used by parties interested in initiating or developing a quality system within an organization. It provides a Quality Control (QC) and Quality Assurance (QA) approach to systems. The starting point was the Dutch Association of Research Quality Assurance (DARQA) Good Laboratory Practice (GLP) committee workshop on 'QA/QC in practice' held on 11 December 1998. Based on the positive feedback expressed for elaboration on this subject, the DARQA GLP committee decided to take the initiative for writing a document that would focus on a practical approach. On 1 July 1999 five working groups, headed by a lead member, had a broad discussion and collected relevant material on 'The role of QC/QA in GLP'. The lead members of each working group then reviewed the findings together with the DARQA GLP committee to begin development of the document. Each working group continued to meet in order to further develop and formulate their results. On 21 March 2000 the lead members met with the involved DARQA GLP committee members to decide on the approach to bring together all information into one document. Mrs Myriam Visschedijk and Mr Rik Hendriks were requested to write the document, based on the

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DOI: 10.1002/qaj.325

results of the working group discussions as summarized by the lead members. The current article is the result of this process.

The text describes both a QC and QA process, considered to be a tool for management, QC and QA responsible personnel. Appendix A is an aid for the implementation by line management.

Introduction

This document provides a general introduction to the differences between QC and QA. It offers practical guidance for the implementation of a QC system and its correlation to the QA program. The Good Clinical Practice (GCP) and the Good Manufacturing Practice (GMP) guidelines consider QC, as well as QA, to be essential parts of the quality system. Although the Organisation for Economic Co-operation and Development (OECD) GLP Principles do not use the term QC or specify any QC activities, the same approach could be applied.

The goal of a quality management program is to incorporate a process of continuous improvement. This is the mission of management, in which QC and QA play an important role. Both QC and QA have a common aim but they achieve it in different ways. QC is involved in standards and limits defined by the environment, which prescribes the rules governing what is correct. In contrast, QA concerns itself with goals and defines what is acceptable. Both aspects are part of the culture of an organization.

Quality is an intrinsic state of mind among staff members and is therefore result-oriented. Management should define study-related and general activities and implement a respective QC and QA model.

Quality has to be delivered by the study personnel and the QA Unit has to assure the quality through an umbrella function. Each staff member of an organization has QC tasks, which are part of the processes to ensure the validity of data. The QA tasks are linked to the QA program, which is independent of the processes.

Definitions

The International Conference on Harmonization (ICH) GCP [1] definitions were adopted as a basis. A few explanatory hints were added to provide guidance in further understanding the content.

QC

According to the ICH GCP definition, QC comprises 'the operational techniques and activities undertaken within the QA system to verify that the requirements for quality of the trial-related activities have been fulfilled' (ICH GCP 1.47):

- objective: process control;
- to ensure quality of the activities;
- measurable: QC data.

QA

According to the ICH GCP definition, QA comprises 'all those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with GCP and the applicable regulatory requirements' (ICH GCP 1.46):

- objective: independent inspection;
- to assure compliance of the process within the quality system;
- measurable: inspection reports.

Factors that Influence the Quality of a Study and How to Make Quality Traceable

The factors that influence the quality of a study define the processes of general and study-related activities within an organization. The study-related activities can be strictly process- or study-based. The general activities can be facility- or process-based (see Figure 1).

This section describes the general as well as the study-related activities. The process can reasonably be divided into six steps: study

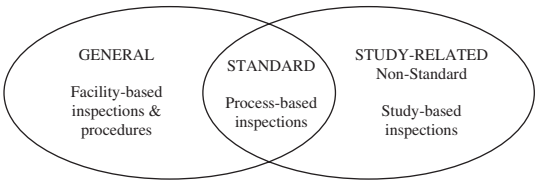

Figure 1. Quality system

Table 1. General activities

Process	General activities	QC	QA
Study preparation	1. Procedures	×	×
	2. Computer system validation	×	×
	3. Management of apparatus	×	×
	4. Instrument validation	×	×
	5. Sample management	×	×
	6. Sample transfer	×	×
	7. Organization and personnel	×	×
	8. Facility	×	×
	9. Laws and regulations		×
	10. QC/QA program		×
Data processing	Deviation handling	×	×
	Computer system validation	×	×
Archiving	Security	×	×
	Access control	×	×
	File management	×	×

preparation, study plan, study performance, data processing, reporting of the study and archiving.

General activities

For general activities QA can perform process- and/or facility-based inspections randomly: The following examples are meant to clarify the QC and QA activities for general items. The actual detailed execution is described in Appendix A. Table 1 provides an overview on the general QC and QA activities.

Study preparation

(1) Procedures

A system should be in place to describe and manage the critical steps of the process. There should be a system for updating standard operating procedures (SOPs) in a timely manner and for communicating all changes to the relevant people.

The content of an SOP is the responsibility of the qualified personnel (author) and of the approving party (management).

- Activity: implementation of a procedure.
- QC: communication and the implementation of a new SOP to applicable personnel.
- QA: inspection of study personnel's training and adherence to the SOP.

(2) Organization and personnel

Line management must ensure that there are sufficient and qualified personnel and that training programs are implemented.

- Activity: documentation of training and experience.
- QC: check for presence and completeness of training records, assessment of training.
- QA: inspection of personnel files.

(3) Equipment

Facility management must ensure that the equipment used in a study is periodically inspected, cleaned, maintained and calibrated according to SOPs and that written records are maintained of all inspection, maintenance, testing, calibration and/or standardizing operations.

- Activity: registration of maintenance information.
- QC: documentation of activity/occurrence.
- QA: inspection of facility and equipment documentation.

Data analysis

Management is responsible to establish procedures to ensure that computerized systems are suitable for their intended purpose and are validated, operated and maintained in accordance with the Principles of GLP.

- Activity: testing of performance qualification.
- QC: control of performance indicators.
- QA: inspection of validation dossier.

Reporting

Procedures within the organization are established to follow both regulatory and internal standards for the content and format of reports.

- Activity: writing the report in accordance with approved procedures.
- QC: review of report text and data for validity and accuracy.
- QA: inspection in accordance with defined procedures as required by regulations.

Archiving

The organization is responsible for providing archives for orderly storage and expedient retrieval of all raw data, documentation, specimens, and reports and for appointing an individual responsible for the coordination of these activities.

- Activity: controlled movement of applicable data, documents etc. into and out of the archives.
- QC: documentation of an item's temporary removal.
- QA: inspection of adherence to procedures on movement of material into and out of the archives.

Study-related activities

For study-related activities QA can perform process- and/or study-based inspections: The following examples are meant to clarify the QC and QA activities for study-related items. The actual detailed application is described in Appendix A. Table 2 provides an overview on the study-related QC and QA activities.

Study preparation

Before a study can start, management and the study director must agree on test item availability, standards, facilities, personnel, statistics, animal models, test guidelines and SOPs, etc.

- Activity: documentation of the characteristics of the test substance.
- QC: verification as to whether the data comply with the specifications.
- QA: no action on a study basis (action will occur under general activities, see Table 1).

Table 2. Study-related activities

Process	Study-related activities	QC	QA
Study preparation	Availability of materials, means and personnel	×	
	Laws and regulations	×	
	QC/QA program	×	
	Request study number	×	
	Study-related SOPs	×	
Study plan	Content study plan as agreed[a]	×	×
	Distribution	×	×
	Change in study plan	×	×
Study performance	Evaluation of critical phases	×	×
Data processing	Witnessing of raw data	×	×
	Processing and validation of results	×	×
	Interpretation of results	×	
Reporting	Raw data		×
	Study file	×	×
	Content of report as agreed[a]		×
Archiving	Delivery of dossier	×	

[a] For example, in accordance with guideline, procedures, contracts.

Study plan

A study starts after the study director and, if applicable, the management and the sponsor sign the study plan (Table 2).

- Activity: receipt of signed study plan.
- QC: documentation of review of the study plan by qualified personnel and, applicable, the sponsor.
- QA: inspection of final signed study plan and effective distribution.

Study performance and data processing

In the raw data all information relevant for the traceability of the study should be documented. Especially in the event of deviations and amendments, the involvement and the decisions of the study director should be clearly documented.

- Activity: performance of the steps specified in the study plan.
- QC: control of data by double data entry, documented witness at selected critical phases, use of spiked samples.

- QA: inspection of selected critical phases, process- and facility-based inspection.

Reporting

The study director is responsible for reporting the study results on the basis of the raw data and for drawing the conclusion.

- Activity: generation of final report.
- QC: check of data in report against raw data.
- QA: random check of data and results for accuracy of reporting, inspection to determine whether the report completely reflects the raw data and protocol requirements.

Archiving

The study director is responsible for the delivery of the study file to the archivist in a timely manner. The archivist is responsible for the documentation and storage of the study dossier.

- Activity: appropriate storage of data in the archive.
- QC: check of completeness of records.
- QA: no action on a study basis (this will occur under general activities, see Table 1).

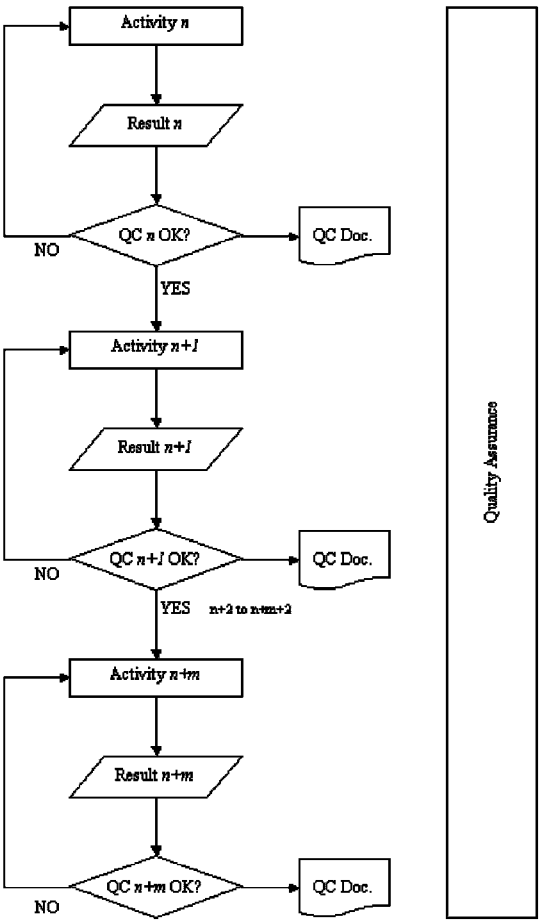

Figure 2. Flowchart for QC and QA

How Can We Make QC Traceable and Verifiable?

Performing QC in practice: how, when and by whom

Although the study director is the single point of study control, the study personnel are responsible for complying with instructions and recording raw data promptly and accurately. This principle of good practices manifests itself through the performance and documentation of QC.

QC is incorporated into each function; it is the check on the quality of the activities within the study and the processes. This check must be traceable and verifiable. Qualified personnel who are involved in the critical phase of the study should perform the QC check.

To control the conduct of a study, QC has to be implemented during the activity. A critical phase can be a single activity or a combination of activities, e.g. preparation of the formulation is a critical phase consisting of several activities: weighing of the test item, homogenizing or dissolving and the determination of the concentration. There is a QC step for each activity. QC is performed on the result of the process, QA is performed on the process itself.

The following process is described in Figure 2:

An activity, as part of the course of a study, produces a result. This result is then checked (QC). If QC shows that the activity was not done appropriately, the activity is redone. When QC confirms the result, the subsequent step or activity can be undertaken. Each QC check is documented.

QC documentation must include the following:

- the person who carried out the QC;

- the date on which the QC was done;
- the items that were checked;
- how items were checked (e.g. as described in a specific study plan or a procedure).

QC is performed within the project, and reported to the relevant responsible person according to documented procedures.

The decision whether to do a QA inspection on this specific QC step is based on a risk assessment of the activity within a critical phase of the study and/or the possible efficiency yield of the inspection at the end of the study process. The process is assured on a random basis by QA.

The QA program and how it relates to QC

QA is a separate responsibility. The goal is to assure the compliance of the study process with regulations. The QA program must therefore be fully independent. Although QA has a reactive inspecting role, it also has a proactive role in improving the quality of the organization. When processes and QC have proved to be an active and reliable system, the organization has reached a higher level of quality (Figure 3).

QC should focus on the results of an activity by controlling each step of data generation.

QA should focus on the result of the critical phase by assuring the processes and the QC of the activities. This can be done through conducting study-, process- or facility-based inspections.

The independent QA program has to include, but is not limited to the following:

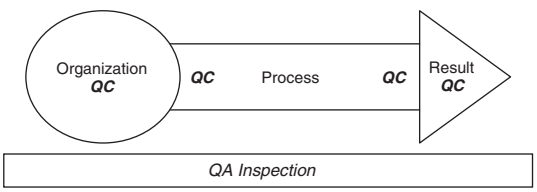

Figure 3. Relationship between QC and QA

- inspections at regular intervals of the QC program;
- inspection of studies and processes at random;
- inspection of the facility at regular intervals;
- advice to management on improving processes.

Appendix A gives examples of activities during the process and of the way QC and QA can be handled. It is up to the organization to make a difference between facility- or process-based inspections and study-related inspection on e.g. the study preparation items.

Conclusion

This paper introduces the concept of a quality system that is completely integrated in an organization, implying that QC and QA tasks are incorporated into the tasks of all employees. Implementing QC in the line organization will give an enormous advantage. The essence, 'right first time', means that the efficiency and quality of the studies will improve. Although the QA program is still independent, the role of QA evolves to monitoring the QC process.

When a quality management system is set up, its implementation may require a change in the corporate culture. From a project management perspective, a quality management system surely helps organizations to continuously improve their processes. This approach aims to define QC not as a separate job but as part of each employee's responsibilities, whereas QA is dedicated to the assurance function during the process.

Acknowledgements

The authors would like to thank all persons that attributed to this document at any stage of its development. This includes – amongst others – Mrs Erna Koelman, Mrs Chris Mitchell, Mr Walter Kafoe and Mr Frans Boersma (members of the DARQA GLP committee), and Mrs Marijke van den Berg, Mr Jan van de Broek, Mr Emiel Termond and Mr Alex Pouwelse (lead members of the working groups).

Appendix A: Examples of QC and QA for the Different Activities Within the Process

Activity		Examples of QC	Examples of QA
Process: study preparation			
Organization and personnel	Organigrams	Check and update of organigrams	Random inspection on QC checks
	Job descriptions	Check job description against practice	Inspection of personnel files
	Assignment study directors (SDs)	Check documented assignment of SD/principal investigator	Inspection of list of SDs/principal investigators
	Training	Check objectives and evaluation	Inspection of training programs
		Check training records	
	Communication (study management)	Check documented planning	
Facilities	Test system facilities	Check on availability of facilities during planning of the study	
	Facilities for handling test and reference items		
	Archive facilities		
	Health and safety/ waste disposal		
	Access control	Check on access control system	Random inspection on process
	House keeping	Check on house keeping and process	Random inspection on process
	Environmental control	Check on environmental conditions (ranges)	Random inspection on process/during study inspection
	Feed/water/bedding supplies	Check on availability and acceptance criteria	Random inspection on process

Activity		Examples of QC	Examples of QA
	Waste handling	Check on correct waste handling process	Random inspection on process
Apparatus (including computerized systems)	Maintenance	Check on maintenance log books	Inspection maintenance process
	Calibration	Check on calibration documentation	Inspection calibration process
	Validation	Check on acceptance criteria (e.g. certificate of release)	Inspection validation process/report
		Check documentation during the validation process for compliance with acceptance criteria	
Materials and reagents	Labelling	Check the content of the label against the certificate	Inspection of labelling
		Check the content of the label against conditions (e.g. temperature/expiry date/health and safety/etc.)	
	Management	Check on minimum stock	Inspection on management of materials and reagents
	Preparation	Check on documentation (weighing, dilution, etc.)	Inspection of preparation
Test system	Ordering	Check documentation on ordering	Inspection ordering process
	Receipt	Check documentation on receipt (acceptance criteria, e.g. health check)	Inspection receipt process (e.g. health check)

Activity		Examples of QC	Examples of QA
	Identification	Check uniqueness of identification	Inspection identification process
	Housing (see facilities)		
Test and reference items	Management (e.g. ordering, receipt, storage, availability)	Check documentation on ordering	Inspection on management
		Check documentation on receipt (acceptance criteria, e.g. certificate of analysis)	
		Check on minimum stock	
	Identification/ Labelling	Check the content of the label against the certificate	Inspection on labelling
		Check the content of the label against conditions (e.g. temperature/expiry date/health and safety/etc.)	
	Formulation	Check/witness on documentation (weighing, dilution, etc.)	Inspection on formulation
	Storage (see facilities)	See facilities	See facilities
Standard operating procedures (SOPs)	Creating procedures	Review of SOPs by all relevant parties	Inspection SOP system (e.g. availability, training, current version, historical procedures, etc.)
	Approval	Approval by all required parties	
	Distribution	Check distribution/ availability	

Activity		Examples of QC	Examples of QA
	Implementation/ training	Check training documentation	
	Application	Check use of current version	
	Management of historical SOPs	Check version control	
		Check availability of historical SOPs	
	Review and/or update cycle	Check need for review/update	
Study plan	Request for study number	Check uniqueness of the code	Inspection on GLP compliance/ adherence to SOPs
	Create study plan	Peer review	
	Communication	Check on availability of resources	
	Critical events/time schedule		Scheduling of inspections
	Distribution	Check proper distribution	
Contract	Outsourcing		Inspection contractors and suppliers
	Selection of suppliers		
	Financial and legal aspects		
Process: study performance in-life			
Test system	Randomization	Check on study plan/SOPs	In-life inspection
	Identification/ handling (e.g. weighing)		Inspection on QC performance and acceptance criteria
	Dose administration		Process/facility inspections
Test item	Formulation analysis	Check accountability Check method for analysis	

Activity		Examples of QC	Examples of QA
	Storage	Check environmental conditions	
Sample management	Collection	Check correctness of samples at sampling (identification, condition)	
	Identification/ labelling		
	Transfer	Check transfer documentation (e.g. chain of custody)	
	Storage	Check environmental conditions	
Waste management	Collection	Check on study plan/ SOPs	
	Transfer		
	Storage/disposal		
Study deviation management	Issuance of deviation or amendment	Check correctness of SOPs and forms for each activity	
	Assess and document any possible impact of deviation	Check adherence to the study plan	
		Check for proper documentation and handling of any deviations	
		Check if any deviation necessitates the update of any SOP	
Process: study performance analysis			
Methods	Validation	Check validation	In-life inspection
		Check used method against method indicated in the study plan	Inspection on QC performance and acceptance criteria
			Process/facility inspections
Equipment	Identification	Check on use of correct equipment	
	QC test before use	Check against acceptance criteria	

Activity		Examples of QC	Examples of QA
Analysis	Sample preparation	Check documentation (dilution, weighing, calculation, identification, etc.)	
	Sample analysis	Check acceptance criteria (e.g. QC samples, parameters, reanalysis, etc.)	
Process: study performance data management (manual and computerized)			
Data management	Collection	Check correctness of provided data (e.g. animal numbers)	Inspection raw data file
		Check on forms of manual data collection	Inspection on QC performance and acceptance criteria
	Transfer	Check on security of transfer	
	Compilation of study file	Check raw data against protocol	
Data analysis	Processing	Check on validated data transfer, audit trail, protection and integrity	
		Check QC data set	
	Interpretation		
Process: reporting			
Issuance of report	Draft report	Check use of correct templates	
		Check transfer of data to report	
		Check completeness/ correctness (100%)	

Activity		Examples of QC	Examples of QA
		Peer review	
		Check for any possible further impact of deviations	
	Final report	Check on QA statement against QA file	Inspection of report
			Inspection on QC performance and acceptance criteria
Process: archiving			
Management	Indexing study file	Check index	Process/facility inspections
	Transfer study file	Check if filed data sets or documentation are complete and correct	
		Check acceptance criteria by archivist (e.g. chain of custody)	
		Check registration of incoming documents	
	Retrieval of files/ access (see facilities)	Check on SOP	
		Check retention times	

Note: QA can always decide to perform facility-, process- or study-based inspections.

Reference

1. Note for Guidance on Good Clinical Practice, CPMP/ICH/135/95. Available at www.ich.org [accessed 3 November 2004].