EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels, 18 November 2009
ENTR/F2/MT/AM/jr D (2009) 37658

EudraLex

The Rules Governing Medicinal Products in the European Union
Volume 4

EU Guidelines to

Good Manufacturing Practice Medicinal Products for Human and Veterinary Use

Part I

Chapter 1 Quality Management System

Draft agreed by GMP/GDP Inspectors Working Group	June 2009
Release for public consultation	18 November 2009
Deadline for comments entr-gmp@ec.europa.eu and ADM-GMDP@ema.europa.eu	31 May 2010
Additional modifications agreed by GMP/GDP Inspectors Working Groups	
Extended deadline for extended comments	
Final text agreed by GMP/GDP Inspectors Working Groups	
Adopted by European Commission	
Deadline for coming into operation	

Some changes have been made to Chapter 1 in order to integrate the principles of "Pharmaceutical Quality System" as described in the ICH Q10 tripartite guideline. The following sections have been added to Chapter 1:
- Quality Management System
- Process Performance and Product Quality Monitoring System and Product Quality Review
- Management of Outsourced Activities and Purchased Materials
- Management of Review on the Quality Management System
- Monitoring of Internal and External Factors Impacting the Quality Management System
- Outcomes of Management Review and Monitoring

Furthermore some amendments to existing sections of the text have been made in order to align with the concepts described in ICH Q10

Principle

The holder of a Manufacturing Authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the relevant Marketing Authorisation(s) and do not place patients at risk due to inadequate safety, quality or efficacy.

An effective quality management system is essential to the realisation of this quality objective reliably, the manufacturer should establish, document, and implement a comprehensively designed and correctly implemented Quality Management System incorporating Good Manufacturing Practice, Quality Assurance, Quality Control and Quality Risk Management principles. The attainment of this quality objective is the responsibility of the organisation's senior management and requires their leadership and the active participation supported by the commitment of staff in many different departments and at all levels within the company, together with the proper supervision of the company's external suppliers of materials and services.

The scope of the guidance in this chapter applies to the technology transfer, manufacture and control and discontinuation of a product. Manufacturers should take account of GMP during the development of products, however this guideline does not specifically apply to the development of a product other than the expectations applicable to the manufacture and control of Investigational Medicinal products.

ICH Q10 as transposed in full into EU GMP as Annex 21 of the guide, provides an example of a pharmaceutical quality system designed for the entire product lifecycle and therefore goes beyond the expectations of this chapter. It should be noted that application of Annex 21 to the entire product life cycle by a company is optional but its use should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development, technology transfer and manufacturing activities, and is therefore supported by Authorities.

Quality Management System

1.1 The Quality Management System should:

i) Achieve Product Realisation

To establish, implement and maintain a system that allows the delivery of products with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with approved regulatory filings) and other internal and external customers.

ii) Establish and Maintain a State of Control

To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes. Quality risk management can be useful in identifying the monitoring and control systems.

iii) Facilitate Continual Improvement

To identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and quality management system enhancements, thereby increasing the ability to fulfil quality needs consistently. Quality risk management can be useful for identifying and prioritising areas for continual improvement.

1.2 The system for managing quality should encompass the organisational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the product will meet its intended specifications for quality and purity.

1.3 Senior management of the manufacturer should ensure that all parts of the Quality Management System are adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. There are additional legal responsibilities for the holder of the Manufacturing Authorisation and for the Qualified Person(s).

1.4 The size and complexity of the manufacturer's activities should be taken into consideration when developing the quality management system or modifying an existing one. The design of the quality management system should incorporate appropriate risk management principles. Some aspects of the quality management system can be company-wide and others site-specific,

1.5 The Quality Management System should be fully documented and its effectiveness monitored. All quality related activities should be defined and documented.

A *Quality Manual* or equivalent documentation approach should be established and should contain the description of the quality management system. The description should include:

(a) The *quality policy*

(b) The scope of the quality management system;

(c) Identification of the quality management system processes, as well as their sequences, linkages and interdependencies. Process maps and flow charts can be useful tools to facilitate depicting quality management system processes in a visual manner;

(d) Management responsibilities within the quality management system

1.6 It is important that the Quality Management System should include a quality unit that is independent of production and that fulfils both certain quality assurance *(QA)* and quality control *(QC)* responsibilities specified in GMP. This Quality Unit can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quality Assurance

1.7 Quality Assurance is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guide.

1.8 The system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that:

(i) medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice;

(ii) production and control operations are clearly specified and Good Manufacturing Practice adopted;

(iii) managerial responsibilities are clearly specified;

(iv) no materials are released or used before the satisfactory completion of evaluation by the quality unit(s). The persons authorised to release starting materials, intermediates and finished product are clearly specified;

(v) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials and the selection and monitoring of their suppliers;

(vi) all quality related activities are recorded at the time they are performed;

(vii) deviation from established procedures are documented and explained. Significant deviations with a potential to affect quality should be investigated, and the investigation and its conclusions are documented. Where necessary, appropriate corrective and/or preventive action (CAPA) should be taken to correct the deviation and to avoid similar deviations occurring in the future. A structured approach to the investigation process should be used with the objective of determining the root cause. There should be effective measures to ensure that CAPA activity is both timely and effective. The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk, in line with the principles of Quality Risk Management described in Annex 20 of this guide. CAPA methodology should result in product and process improvements and enhanced product and process understanding;

(viii) there are procedures for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, deviations, product defects and related actions (e.g. quality related complaints, recalls, regulatory actions, etc.).;

(ix) all changes including CAPA activity, that have the potential to affect product quality are introduced in a managed way in accordance with the appropriate regulatory scrutiny demanded by the region to which the product will be supplied. Steps should be taken to ensure that all are compatible with the granted marketing authorisation where appropriate. After implementation, an evaluation of the change should be undertaken to confirm the change objectives were achieved and that there was no deleterious impact on product quality;

(x) all necessary controls on intermediate products, and any other in-process controls and validations are carried out;

(xi) the finished product is correctly processed and checked, according to the defined procedures;

(xii) medicinal products are not sold or supplied before a Qualified Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal
products;

(xiii) satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;

(xiv) there is a procedure for Self-Inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Quality Assurance system;

(xv) there are formal systems in place for the periodic review of operation of the quality management system and to identify opportunities for continual improvement.

Good Manufacturing Practice for Medicinal Products (GMP)

1.8 Good Manufacturing Practice is that part of the Quality Management system which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation or product specification. Good Manufacturing Practice is concerned with both production and quality control.

1.9 The basic requirements of GMP are that:

(i) all manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;

(ii) critical steps of manufacturing processes and significant changes to the process are validated;

(iii) all necessary facilities for GMP are provided including:

- appropriately qualified and trained personnel;
- adequate premises and space;
- suitable equipment and services;
- correct materials, containers and labels;
- approved procedures and instructions;
- suitable storage and transport;

(iv) instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;

(v) operators are trained to carry out procedures correctly;

(vi) records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated and appropriate CAPA actioned;

(vii) records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

(viii) the distribution (wholesaling) of the products minimises any risk to their quality;

(ix) a system is available to recall any batch of product, from sale or supply;

(x) complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent reoccurrence.

Quality Control

1.10 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, 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.

1.11 The basic requirements of Quality Control are that:
(i) adequate facilities, trained personnel and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;

(ii) samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by Quality Control;

(iii) test methods are validated;

(iv) records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;

(v) the finished products contain active ingredients complying with the qualitative and quantitative composition of the Marketing Authorisation, are of the purity required, and are enclosed within their proper containers and correctly labelled;

(vi) records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;

(vii) no batch of product is released for sale or supply prior to certification by a Qualified Person that it is in accordance with the requirements of the relevant authorisations;

(viii) sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

Process Performance and Product Quality Monitoring System and Product Quality Review

1.12 Pharmaceutical companies should plan and execute a system for the monitoring of process performance and product quality to ensure a state of control is maintained. An effective monitoring system provides assurance of the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement. The process performance and product quality monitoring and review system should:

(a) Use quality risk management to establish the control strategy. This can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. The control strategy should facilitate timely *feedback / feed forward* and appropriate corrective action and preventive action;

(b) Provide the tools for measurement and analysis of parameters and attributes identified in the control strategy (e.g., data management and statistical tools);

(c) Analyse parameters and attributes identified in the control strategy to verify continued operation within a state of control;

(d) Identify sources of variation affecting process performance and product quality for potential continual improvement activities to reduce or control variation;

(e) Include feedback on product quality from both internal and external sources, e.g., complaints, product rejections, non-conformances, recalls, deviations, audits and regulatory inspections and findings;

(f) Provide knowledge to enhance process understanding, enrich the *design space* (where established), and enable innovative approaches to process validation.

1.13 Regular periodic or rolling quality reviews of all licensed medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

(i) a review of starting materials including packaging materials used in the product, especially those from new sources.

(ii) a review of critical in-process controls and finished product results.

(iii) a review of all batches that failed to meet established specification(s) and their investigation.

(iv) a review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.

(v) a review of all changes carried out to the processes or analytical methods.

(vi) a review of Marketing Authorisation variations submitted/granted/refused, including those for third country (export only) dossiers.

(vii) a review of the results of the stability monitoring programme and any adverse trends.

(viii) a review of all quality-related returns, complaints and recalls and the investigations performed at the time.

(ix) a review of adequacy of any other previous product process or equipment corrective actions.

(x) for new marketing authorisations and variations to marketing authorisations, a review of post-marketing commitments.

(xi) the qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.

(xii) a review of any contractual arrangements as defined in Chapter 7 to ensure that they are up to date.

The manufacturer and marketing authorisation holder should evaluate the results of this review, where different, and an assessment made of whether corrective and preventative action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventative actions should be completed in a timely and effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self inspection.

Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. where scientifically justified. Where the marketing authorisation holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The Qualified Person responsible for final batch certification together with the marketing authorisation holder should ensure that the quality review is performed in a timely manner and is accurate.

Management of Outsourced Activities and Purchased Materials

1.14 The quality management system, including the management responsibilities described in Chapter 2, extends to the control and review of any outsourced activities and quality of purchased materials. The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials. These processes should incorporate quality risk management and include:
(a) Assessing prior to outsourcing operations or selecting material suppliers, the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (e.g., audits, material evaluations, qualification);

(b) Defining the responsibilities and communication processes for quality-related activities of the involved parties. For outsourced activities, this should be included in a written agreement between the contract giver and contract acceptor;
(c) Monitoring and review of the performance of the contract acceptor or the quality of the material from the provider, and the identification and implementation of any needed improvements;
(d)Monitoring incoming ingredients and materials to ensure they are from approved sources using the agreed supply chain.

Management Review of the Quality Management System

1.15 Management should have a formal process for reviewing the quality management system on a periodic basis. The review should include:
(a) Measurement of achievement of quality management system objectives;
(b) Assessment of performance indicators that can be used to monitor the effectiveness of processes within the quality management system, such as:

(1) Complaint, deviation, CAPA and change management processes;
(2) Feedback on outsourced activities;
(3) Self-assessment processes including risk assessments, trending, and audits;
(4) External assessments such as regulatory inspections and findings and customer audits.

Monitoring of Internal and External Factors Impacting the Quality Management System

1.16 Factors monitored by management can include:
(a) Emerging regulations, guidance and quality issues that can impact the Quality Management System;
(b) Innovations that might enhance the quality management system;
(c) Changes in business environment and objectives;
(d) Changes in product ownership.

Outcomes of Management Review and Monitoring

1.17 The outcome of management review of the quality management system and monitoring of internal and external factors can include:
(a) Improvements to the quality management system and related processes;
(b) Allocation or reallocation of resources and/or personnel training;
(c) Revisions to quality policy and quality objectives;
(d) Documentation and timely and effective communication of the results of the management review and actions, including escalation of appropriate issues to senior management.

Quality Risk Management

1.18 Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

1.19 The quality risk management system should ensure that:
- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient

- the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk

Examples of the processes and applications of quality risk management can be found inter alia in Annex 20.