EUROPEAN COMMISSION
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health Systems and Products
Medicinal Products - Quality, safety and efficacy

Brussels,
SANCO/AM/sl/ddg1.d.6(2012)860362

EudraLex

The Rules Governing Medicinal Products in the European Union

Volume 4

EU Guidelines for

Good Manufacturing Practice for

Medicinal Products for Human and Veterinary Use

Chapter 1
Pharmaceutical Quality System

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.

Status of the document: revision 3

Reasons for changes: Amendments to the text of Chapter 1 have been made in order to align with the concepts and terminology described in the ICH Q10 tripartite guideline on Pharmaceutical Quality System. The title of the chapter itself is also changed accordingly.

Deadline for coming into operation: 31 January 2013

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 Marketing Authorisation or Clinical Trial Authorisation, as appropriate and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by its distributors. To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented Pharmaceutical Quality System[1] incorporating Good Manufacturing Practice and Quality Risk Management. It should be fully documented and its effectiveness monitored. All parts of the Pharmaceutical Quality System should be 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).

The basic concepts of Quality Management, Good Manufacturing Practice and Quality Risk Management are inter-related. They are described here in order to emphasise their relationships and their fundamental importance to the production and control of medicinal products.

Pharmaceutical Quality System[1]

1.1 Quality Management 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 Management therefore incorporates Good Manufacturing Practice.

1.2 GMP applies to the lifecycle stages from the manufacture of investigational medicinal products, technology transfer, commercial manufacturing through to product discontinuation. However the Pharmaceutical Quality System can extend to the pharmaceutical development lifecycle stage as described in ICH Q10, which while optional, should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities. ICH Q10 is reproduced in Part III of the Guide and can be used to supplement the contents of this chapter.

1.3 The size and complexity of the company's activities should be taken into consideration when developing a new Pharmaceutical Quality System or modifying an existing one. The design of the system should incorporate appropriate risk management principles including the use of appropriate tools. While some aspects of the system can be company-wide and others site-specific, the effectiveness of the system is normally demonstrated at the site level.

[1] Art 6 of Directives 2003/94/EC and 91/412/EEC require manufacturers to establish and implement an effective pharmaceutical quality assurance system. The term Pharmaceutical Quality System is used in this chapter in the interests of consistency with ICH Q10 terminology. For the purposes of this chapter these terms can be considered interchangeable.

1.4 A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that:

(i) Product realisation is achieved by designing, planning, implementing, maintaining and continuously improving a system that allows the consistent delivery of products with appropriate quality attributes;

(ii) Product and process knowledge is managed throughout all lifecycle stages;

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

(iv) Production and control operations are clearly specified and Good Manufacturing Practice adopted;

(v) Managerial responsibilities are clearly specified;

(vi) Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials, the selection and monitoring of suppliers and for verifying that each delivery is from the approved supply chain;

(vii) Processes are in place to assure the management of outsourced activities.

(viii) A state of control is established and maintained by developing and using effective monitoring and control systems for process performance and product quality.

(ix) The results of product and processes monitoring are taken into account in batch release, in the investigation of deviations, and, with a view to taking preventive action to avoid potential deviations occurring in the future.

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

(xi) Continual improvement is facilitated through the implementation of quality improvements appropriate to the current level of process and product knowledge.

(xii) Arrangements are in place for the prospective evaluation of planned changes and their approval prior to implementation taking into account regulatory notification and approval where required;

(xiii) After implementation of any change, an evaluation is undertaken to confirm the quality objectives were achieved and that there was no unintended deleterious impact on product quality;

(xiv) An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems. This can be determined using Quality Risk Management principles. In cases

where the true root cause(s) of the issue cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those. Where human error is suspected or identified as the cause, this should be justified having taken care to ensure that process, procedural or system-based errors or problems have not been overlooked, if present. Appropriate corrective actions and/or preventative actions (CAPAs) should be identified and taken in response to investigations. The effectiveness of such actions should be monitored and assessed, in line with Quality Risk Management principles.

(xv) 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;

(xvi) 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;

(xvii) There is a process for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Pharmaceutical Quality System.

1.5 Senior management has the ultimate responsibility to ensure an effective Pharmaceutical Quality System is in place, adequately resourced and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management's leadership and active participation in the Pharmaceutical Quality System is essential. This leadership should ensure the support and commitment of staff at all levels and sites within the organisation to the Pharmaceutical Quality System.

1.6 There should be periodic management review, with the involvement of senior management, of the operation of the Pharmaceutical Quality System to identify opportunities for continual improvement of products, processes and the system itself.

1.7 The Pharmaceutical Quality System should be defined and documented. A Quality Manual or equivalent documentation should be established and should contain a description of the quality management system including management responsibilities.

Good Manufacturing Practice for Medicinal Products

1.8 Good Manufacturing Practice is that part of Quality Management 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, Clinical Trial Authorisation or product specification. Good Manufacturing Practice is concerned with both production and quality control. 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, in accordance with the Pharmaceutical Quality System;
- 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) Procedures are carried out correctly and operators are trained to do so;

(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.

(vii) Any significant deviations are fully recorded, investigated with the objective of determining the root cause and appropriate corrective and preventive action implemented;

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

(ix) The distribution of the products minimises any risk to their quality and takes account of Good Distribution Practice;

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

(xi) Complaints about 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

1.9 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. The basic requirements of Quality Control are that:

(i) Adequate facilities, trained personnel and approved procedures are available for sampling 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 approved personnel and methods;

(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 or clinical trial 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 in accordance with annex 16;

(viii) Sufficient reference samples of starting materials and products are retained in accordance with Annex 19 to permit future examination of the product if necessary and that the sample is retained in the final pack.

Product Quality Review

1.10 Regular periodic or rolling quality reviews of all authorised 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 and in particular the review of supply chain traceability of active substances.

(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 preventive 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 or 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.

1.11 The manufacturer and, where different, marketing authorisation holder should evaluate the results of the review and an assessment made as to whether corrective and preventive action or any revalidation should be undertaken, under the Pharmaceutical Quality System. 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 product quality review.

Quality Risk Management

1.12 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.

1.13 The principles of quality risk management are that:

i) 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

ii) 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 ICH Q9 which is reproduced in Part III of the Guide.