



EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels, 25 October 2005

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 6 Quality Control

Document History	
Revision to include new Chapter on On-going Stability Programme and adjust Section 6.14 on reference samples	October 2005
Date of revised version coming into operation	01 June 2006

Table of Contents

Principle

General

Good Quality Control Laboratory Practice

Documentation

Sampling

Testing

On-going Stability Programme

Principle

Quality Control is concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality Control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control.

(see also Chapter 1).

General

- 6.1 Each holder of a manufacturing authorisation should have a Quality Control Department. This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.
- 6.2 The principal duties of the head of Quality Control are summarised in Chapter 2. The Quality Control Department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, keep the reference samples of materials and products, ensure the correct labelling of containers of materials and products, ensure the monitoring of the stability of the products, participate in the investigation of complaints related to the quality of the product, etc. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.
- 6.3 Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the final finished pack.
- 6.4 Quality Control personnel should have access to production areas for sampling and investigation as appropriate.

Good Quality Control Laboratory Practice

- 6.5 Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3.
- 6.6 The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed in Chapter 7, Contract Analysis, can be accepted for particular reasons, but this should be stated in the Quality Control records.

Documentation

- 6.7 Laboratory documentation should follow the principles given in Chapter 4. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department:
- specifications;
 - sampling procedures;
 - testing procedures and records (including analytical worksheets and/or laboratory notebooks);
 - analytical reports and/or certificates;
 - data from environmental monitoring, where required;
 - validation records of test methods, where applicable;
 - procedures for and records of the calibration of instruments and maintenance of equipment.
- 6.8 Any Quality Control documentation relating to a batch record should be retained for one year after the expiry date of the batch and at least 5 years after the certification referred to in Article 51(3) of Directive 2001/83/EC.
- 6.9 For some kinds of data (e.g. analytical tests results, yields, environmental controls) it is recommended that records are kept in a manner permitting trend evaluation.
- 6.10 In addition to the information which is part of the batch record, other original data such as laboratory notebooks and/or records should be retained and readily available

Sampling

- 6.11 The sample taking should be done in accordance with approved written procedures that describe:
- the method of sampling;
 - the equipment to be used;
 - the amount of the sample to be taken;
 - instructions for any required sub-division of the sample;
 - the type and condition of the sample container to be used;
 - the identification of containers sampled;

- any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
 - the storage conditions;
 - instructions for the cleaning and storage of sampling equipment.
- 6.12 Reference samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process).
- 6.13 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn.
- 6.14 Further guidance on reference and retention samples is given in Annex 19.

Testing

- 6.15 Analytical methods should be validated. All testing operations described in the marketing authorisation should be carried out according to the approved methods.
- 6.16 The results obtained should be recorded and checked to make sure that they are consistent with each other. Any calculations should be critically examined.
- 6.17 The tests performed should be recorded and the records should include at least the following data:
- a) name of the material or product and, where applicable, dosage form;
 - b) batch number and, where appropriate, the manufacturer and/or supplier;
 - c) references to the relevant specifications and testing procedures;
 - d) test results, including observations and calculations, and reference to any certificates of analysis;
 - e) dates of testing;
 - f) initials of the persons who performed the testing;
 - g) initials of the persons who verified the testing and the calculations, where appropriate;
 - h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.
- 6.18 All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.
- 6.19 Special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media. They should be prepared in accordance with written procedures.
- 6.20 Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardisation and the last current factor should be indicated.
- 6.21 Where necessary, the date of receipt of any substance used for testing operations (e.g.

reagents and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

- 6.22 Animals used for testing components, materials or products, should, where appropriate, be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use.

On-going stability programme

- 6.23 After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of impurities or dissolution profile) associated with the formulation in the marketed package.

- 6.24 The purpose of the on-going stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.

- 6.25 This mainly applies to the medicinal product in the package in which it is sold, but consideration should also be given to the inclusion in the programme of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored on an on-going basis. However, when relevant, the stability of reconstituted product can also be monitored.

- 6.26 The on-going stability programme should be described in a written protocol following the general rules of Chapter 4 and results formalised as a report. The equipment used for the on-going stability programme (stability chambers among others) should be qualified and maintained following the general rules of Chapter 3 and annex 15.

- 6.27 The protocol for an on-going stability programme should extend to the end of the shelf life period and should include, but not be limited to, the following parameters:

- number of batch(es) per strength and different batch sizes, if applicable
- relevant physical, chemical, microbiological and biological test methods
- acceptance criteria
- reference to test methods
- description of the container closure system(s)
- testing intervals (time points)
- description of the conditions of storage (standardised ICH conditions for long term testing, consistent with the product labelling, should be used)
- other applicable parameters specific to the medicinal product.

- 6.28 The protocol for the on-going stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorisation dossier

provided that this is justified and documented in the protocol (for example the frequency of testing, or when updating to ICH recommendations).

- 6.29 The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year). For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk-benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.
- 6.30 In certain situations, additional batches should be included in the on-going stability programme. For example, an on-going stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.
- 6.31 Results of on-going stability studies should be made available to key personnel and, in particular, to the Qualified Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned. Results of on-going stability studies should be available at the site of manufacture for review by the competent authority.
- 6.32 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with chapter 8 of the GMP Guide and in consultation with the relevant competent authorities.
- 6.33. A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.