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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**

**Part 1
Chapter 6: Quality Control**

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

Reasons for changes:

Inclusion of a new section on technical transfer of testing methods and other items such as Out Of Specification results.

Deadline for coming into operation: <6 months from publication>

Principle

This chapter should be read in conjunction with all relevant sections of the GMP guide

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.

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, oversee the control of the reference and/or retention samples of materials and products when applicable, 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. Laboratory equipment should not be routinely moved between high risk areas to avoid accidental cross-contamination. In particular, the microbiological laboratory should be arranged so as to minimize risk of cross-contamination.
- 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:
 - i. Specifications;

- ii. Procedures describing sampling, testing, records (including test worksheets and/or laboratory notebooks), recording and verifying;
 - iii. Procedures for and records of the calibration/qualification of instruments and maintenance of equipment;
 - iv. A procedure for the investigation of Out of Specification and Out Of Trend results;
 - v. Testing reports and/or certificates of analysis;
 - vi. Data from environmental (air, water and other utilities) monitoring, where required;
 - vii. Validation records of test methods, where applicable.
- 6.8 Any Quality Control documentation relating to a batch record should be retained following the principles given in chapter 4 on retention of batch documentation.
- 6.9 Some kinds of data (e.g. tests results, yields, environmental controls) should be recorded in a manner permitting trend evaluation. Any out of trend or out of specification data should be addressed and subject to investigation.
- 6.10 In addition to the information which is part of the batch documentation, other raw data such as laboratory notebooks and/or records should be retained and readily available

Sampling

- 6.11 The sample taking should be done and recorded in accordance with approved written procedures that describe:
- i. The method of sampling;
 - ii. The equipment to be used;
 - iii. The amount of the sample to be taken;
 - iv. Instructions for any required sub-division of the sample;
 - v. The type and condition of the sample container to be used;
 - vi. The identification of containers sampled;
 - vii. Any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
 - viii. The storage conditions;
 - ix. Instructions for the cleaning and storage of sampling equipment.
- 6.12 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). The sampling plan used should be appropriately justified and based on a risk management approach.
- 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. They should be managed in a manner to minimize the risk of mix-up and to protect the samples from adverse storage conditions.
- 6.14 Further guidance on reference and retention samples is given in Annex 19.

Testing

- 6.15 Testing methods should be validated. A laboratory that is using a testing method and which did not perform the original validation, should verify the appropriateness of the testing method. All testing operations described in the marketing authorisation or technical dossier should be carried out according to the approved methods.
- 6.16 The results obtained should be recorded. Results of parameters identified as quality attribute or as critical should be trended 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:
- i. Name of the material or product and, where applicable, dosage form;
 - ii. Batch number and, where appropriate, the manufacturer and/or supplier;
 - iii. References to the relevant specifications and testing procedures;
 - iv. Test results, including observations and calculations, and reference to any certificates of analysis;
 - v. Dates of testing;
 - vi. Initials of the persons who performed the testing;
 - vii. Initials of the persons who verified the testing and the calculations, where appropriate;
 - viii. A clear statement of approval or rejection (or other status decision) and the dated signature of the designated responsible person;
 - ix. Reference to the equipment used.
- 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, solutions, glassware, reference standards and culture media. They should be prepared and controlled in accordance with written procedures. The level of controls should be commensurate to their use and to the available stability data.
- 6.20 Reference standards should be established as suitable for their intended use. Their qualification and certification as such should be clearly stated and documented. Whenever compendial reference standards from an officially recognised source exist, these should preferably be used as primary reference standards unless fully justified (the use of secondary standards is permitted once their traceability to primary standards has been demonstrated and is documented). These compendial materials should be used for the purpose described in the appropriate monograph unless otherwise authorised by the National Competent Authority.
- 6.21 Laboratory reagents, solutions, reference standards and culture media should be marked with the preparation and opening date and the signature of the person who prepared them. The expiry date of 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.
- 6.22 Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents, solutions 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.

- 6.23 Culture media should be prepared in accordance with the media manufacturer's requirements unless scientifically justified. The performance of all culture media should be verified prior to use.
- 6.24 Used microbiological media and strains should be decontaminated according to a standard procedure and disposed of in a manner to prevent the cross-contamination and retention of residues. The in-use shelf life of microbiological media should be established, documented and scientifically justified.
- 6.25 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

- 6.26 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.
- 6.27 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.
- 6.28 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.
- 6.29 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.
- 6.30 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:
 - i. Number of batch(es) per strength and different batch sizes, if applicable;
 - ii. Relevant physical, chemical, microbiological and biological test methods;
 - iii. Acceptance criteria;
 - iv. Reference to test methods;
 - v. Description of the container closure system(s);
 - vi. Testing intervals (time points);
 - vii. Description of the conditions of storage (standardised ICH/VICH conditions for long

term testing, consistent with the product labelling, should be used);

viii. Other applicable parameters specific to the medicinal product.

- 6.31 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/VICH recommendations).
- 6.32 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.
- 6.33 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.
- 6.34 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.
- 6.35 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, affecting product batches released on the market 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.
- 6.36 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.

Technical transfer of testing methods

- 6.37 Prior to transferring a test method, the transferring site should verify that the test method(s) comply with those as described in the Marketing Authorisation or the relevant technical dossier. The original validation of the test method(s) should be reviewed to ensure compliance with current ICH/VICH requirements. A gap analysis should be performed and documented to identify any supplementary validation that should be performed, prior to commencing the technical transfer process.
- 6.38 The transfer of testing methods from one laboratory (transferring laboratory) to another laboratory (receiving laboratory) should be described in a detailed protocol.
- 6.39 The transfer protocol should include, but not be limited to, the following parameters:
- i. Identification of the testing to be performed and the relevant test method(s) undergoing transfer;
 - ii. Identification of the additional training requirements;

- iii. Identification of standards and samples to be tested;
 - iv. Identification of any special transport and storage conditions of test items;
 - v. The acceptance criteria which should be based upon the current validation study of the methodology and with respect to ICH/VICH requirements.
- 6.40 Deviations from the protocol should be investigated prior to closure of the technical transfer process. The technical transfer report should document the comparative outcome of the process and should identify areas requiring further test method revalidation, if applicable.
- 6.41 Where appropriate, specific requirements described in others European Guidelines, should be addressed for the transfer of particular testing methods (e.g Near Infrared Spectroscopy).