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The Rules Governing Medicinal Products in the European Union

EU Guidelines to
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Introduction

Document History	
The <i>first edition</i> of the Guide was published, including an annex on the manufacture of sterile medicinal products.	1989
The <i>second edition</i> was published; implementing Commission Directives 91/356 of 13 June 1991 and 91/412 of 23 July 1991 laying down the principles and guidelines on good manufacturing practice for medicinal products for human use as well as for veterinary medicinal products. The second edition also included 12 additional annexes.	January 1992
An update of legal references was made. In the meantime, the guide is updated as needed on the website of the European Commission, several additional annexes added.	August 2004
Re-structuring of GMP guide, consisting of Part I for medicinal products for human and veterinary use and Part II for active substances used as starting materials, implementing Directives 2004/27/EC and 2004/28/EC. The current guide includes 17 Annexes, the former Annex 18 being replaced.	October 2005
Update of the text and introduction of a new Part III	December 2010

Introduction

The pharmaceutical industry of the European Union maintains high standards of Quality Management in the development, manufacture and control of medicinal products. A system of marketing authorisations ensures that all medicinal products are assessed by a competent authority to ensure compliance with contemporary requirements of safety, quality and efficacy. A system of manufacturing authorisations ensures that all products authorised on the European market are manufactured/ imported only by authorised manufacturers, whose activities are regularly inspected by the competent authorities, using Quality Risk Management principles. Manufacturing authorisations are required by all pharmaceutical manufacturers in the European Union whether the products are sold within or outside of the Union.

Two directives laying down principles and guidelines of good manufacturing practice (GMP) for medicinal products were adopted by the Commission. Directive 2003/94/EC applies to medicinal products for human use and Directive 91/412/EEC for veterinary use. Detailed guidelines in accordance with those principles are published in the Guide to Good Manufacturing Practice which will be used in assessing applications for manufacturing authorisations and as a basis for inspection of manufacturers of medicinal products.

The principles of GMP and the detailed guidelines are applicable to all operations which require the authorisations referred to in Article 40 of Directive 2001/83/EC, in Article 44 of Directive 2001/82/EC and Article 13 of Directive 2001/20/EC, as amended. They are also relevant for pharmaceutical manufacturing processes, such as that undertaken in hospitals.

All Member States and the industry agreed that the GMP requirements applicable to the manufacture of veterinary medicinal products are the same as those applicable to the manufacture of medicinal products for human use. Certain detailed adjustments to the GMP guidelines are set out in two annexes specific to veterinary medicinal products and to immunological veterinary medicinal products.

The Guide is presented in three parts and supplemented by a series of annexes. Part I covers GMP principles for the manufacture of medicinal products. Part II covers GMP for active substances used as starting materials. Part III contains GMP related documents, which clarify regulatory expectations.

Chapters of Part I on “basic requirements” are headed by principles as defined in Directives 2003/94/EC and 91/412/EEC. Chapter 1 on Quality Management outlines the fundamental concept of quality management as applied to the manufacture of medicinal products. Thereafter, each chapter has a principle outlining the quality management objectives of that chapter and a text which provides sufficient detail for manufacturers to be made aware of the essential matters to be considered when implementing the principle.

According to the revised Article 47 and Article 51, respectively, of the Directive 2001/83/EC and Directive 2001/82/EC, as amended, detailed guidelines on the principles of GMP for active substances used as starting materials shall be adopted and published by the Commission. Part II was established on the basis of a guideline developed on the level of ICH and published as ICH Q7A on “active pharmaceutical ingredients”. It has an extended application both for the human and the veterinary sector.

In addition to the general matters of Good Manufacturing Practice outlined in Part I and II, a series of annexes providing detail about specific areas of activity is included. For some manufacturing processes, different annexes will apply simultaneously (e.g. annex on sterile preparations and on radiopharmaceuticals and/or on biological medicinal products).

A glossary of some terms used in the Guide has been incorporated after the annexes. Part III is intended to host a collection of GMP related documents, which are not detailed guidelines on the principles of GMP laid down in Directives 2003/94/EC and 91/412/EC. The aim of Part III is to clarify regulatory expectations and it should be viewed as a source of information on current best practices. Details on the applicability will be described separately in each document.

The Guide is not intended to cover safety aspects for the personnel engaged in manufacture. This may be particularly important in the manufacture of certain medicinal products such as highly active, biological and radioactive medicinal products. However, those aspects are governed by other provisions of Union or national law.

Throughout the Guide, it is assumed that the requirements of the Marketing Authorisation relating to the safety, quality and efficacy of the products, are systematically incorporated into all the manufacturing, control and release for sale arrangements of the holder of the Manufacturing Authorisation.

For many years, the manufacture of medicinal products has taken place in accordance with guidelines for Good Manufacturing Practice and the manufacture of medicinal products is not governed by CEN/ISO standards. The CEN/ISO standards have been considered but the terminology of these standards has not been implemented in this edition. It is recognised that there are acceptable methods, other than those described in the Guide, which are capable of achieving the principles of Quality Management. The Guide is not intended to place any restraint upon the development of any new concepts or new technologies which have been validated and which provide a level of Quality Management at least equivalent to those set out in this Guide.

The GMP guide will be regularly revised in order to reflect continual improvement of best practices in the field of Quality. Revisions will be made publicly available on the website of the European Commission:

http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm



EUROPEAN COMMISSION
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Health Systems and Products
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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

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 System¹ 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 System¹

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.



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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 2: Personnel

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^a

Reasons for changes: Changes have been made in order to integrate the principles of “Pharmaceutical Quality System” as described in the ICH Q10 tripartite guideline. A section has been added on consultants

Deadline for coming into operation: 16 February 2014

Principle

The correct manufacture of medicinal products relies upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

General

2.1 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. Senior management should determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the quality management system and continually improve its effectiveness. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

2.2 The manufacturer must have an organisation chart in which the relationships between the heads of Production, Quality Control and where applicable Head of Quality Assurance or Quality Unit referred to in point 2.5 and the position of the Qualified Person(s) are clearly shown in the managerial hierarchy.

2.3 People in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice.

2.4 Senior management has the ultimate responsibility to ensure an effective quality management system is in place to achieve the *quality objectives*, and, that roles, responsibilities, and authorities are defined, communicated and implemented throughout the organisation. Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality and should ensure continuing suitability and effectiveness of the quality management system and GMP compliance through participation in management review.

Key Personnel

2.5 Senior Management should appoint Key Management Personnel including the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the duties described in Article 51 of Directive 2001/83/EC¹, an adequate number, but at least one, Qualified Person(s) designated for the purpose. Normally, key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent from each other. In large organisations, it may be necessary to delegate some of the functions listed in 2.7, 2.8 and 2.9. Additionally depending on the size and organisational structure of the company, a separate Head of Quality Assurance or Head of the Quality Unit may be appointed. Where such a function exists usually some of the responsibilities described in 2.7, 2.8 and 2.9 are shared with the Head of Quality Control and Head of Production and

¹ Article 55 of Directive 2001/82/EC

senior management should therefore take care that roles, responsibilities, and authorities are defined.

2.6 The duties of the Qualified Person(s) are described in Article 51 of Directive 2001/83/EC, and can be summarised as follows:

a) for medicinal products manufactured within the European Union, a Qualified Person must ensure that each batch has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorisation²;

(b) in the case of medicinal products coming from third countries, irrespective of whether the product has been manufactured in the European Union a Qualified Person must ensure that each production batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation. The Qualified Person must certify in a register or equivalent document, as operations are carried out and before any release, that each production batch satisfies the provisions of Article 51.

The persons responsible for these duties must meet the qualification requirements laid down in Article 49³ of the same Directive, they shall be permanently and continuously at the disposal of the holder of the Manufacturing Authorisation to carry out their responsibilities.

The responsibilities of a Qualified Person may be delegated, but only to other Qualified Person(s).

Guidance on the role of the Qualified Person is elaborated in Annex 16.

2.7 The head of the Production Department generally has the following responsibilities:

- i. To ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
- ii. To approve the instructions relating to production operations and to ensure their strict implementation;
- iii. To ensure that the production records are evaluated and signed by an authorised person;
- iv. To ensure the qualification and maintenance of his department, premises and equipment;
- v. To ensure that the appropriate validations are done;
- vi. To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

2.8 The head of Quality Control generally has the following responsibilities:

- i. To approve or reject, as he sees fit, starting materials, packaging materials, intermediate, bulk and finished products;
- ii. To ensure that all necessary testing is carried out and the associated records evaluated;

² According to Article 51 paragraph 1 of Directive 2001/83/EC, the batches of medicinal products which have undergone such controls in a Member State shall be exempt from the controls if they are marketed in another Member State, accompanied by the control reports signed by the qualified person..

³ Article 53 of Directive 2001/82/EC

- iii. To approve specifications, sampling instructions, test methods and other Quality Control procedures;
- iv. To approve and monitor any contract analysts;
- v. To ensure the qualification and maintenance of his department, premises and equipment;
- vi. To ensure that the appropriate validations are done;
- vii. To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

Other duties of Quality Control are summarised in Chapter 6.

2.9 The heads of Production, Quality Control and where relevant, Head of Quality Assurance or Head of Quality Unit, generally have some shared, or jointly exercised, responsibilities relating to quality including in particular the design, effective implementation, monitoring and maintenance of the quality management system. These may include, subject to any national regulations:

- i. The authorisation of written procedures and other documents, including amendments;
- ii. The monitoring and control of the manufacturing environment;
- iii. Plant hygiene;
- iv. Process validation;
- v. Training;
- vi. The approval and monitoring of suppliers of materials;
- vii. The approval and monitoring of contract manufacturers and providers of other GMP related outsourced activities;
- viii. The designation and monitoring of storage conditions for materials and products;
- ix. The retention of records;
- x. The monitoring of compliance with the requirements of Good Manufacturing Practice;
- xi. The inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality;
- xii. Participation in management reviews of process performance, product quality and of the quality management system and advocating continual improvement
- xiii. Ensuring that a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management.

Training

2.10 The manufacturer should provide training for all the personnel whose duties take them into production and storage areas or into control laboratories (including the technical, maintenance and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

2.11 Besides the basic training on the theory and practice of the quality management system and Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programmes should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.

2.12 Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitising materials are handled, should be given specific training.

2.13 Visitors or untrained personnel should, preferably, not be taken into the production and quality control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.

2.14 The pharmaceutical quality system and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

Personnel Hygiene

2.15 Detailed hygiene programmes should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices and clothing of personnel. These procedures should be understood and followed in a very strict way by every person whose duties take him into the production and control areas. Hygiene programmes should be promoted by management and widely discussed during training sessions.

2.16 All personnel should receive medical examination upon recruitment. It must be the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the manufacturer's knowledge. After the first medical examination, examinations should be carried out when necessary for the work and personal health.

2.17 Steps should be taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of medicinal products.

2.18 Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.

2.19 Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials or personal medication in the production and storage areas should be prohibited. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected should be forbidden.

2.20 Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.

2.21 Personnel should be instructed to use the hand-washing facilities.

2.22 Any specific requirements for the manufacture of special groups of products, for example sterile preparations, are covered in the annexes.

Consultants

2.23 Consultants should have adequate education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

CHAPTER 3 PREMISES AND EQUIPMENT

Principle

Premises and equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimise the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products.

Premises

General

- 3.1 Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.
- 3.2 Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.
- 3.3 Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.
- 3.4 Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.
- 3.5 Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

Production Area

- 3.6 In order to minimise the risk of a serious medical hazard due to cross-contamination, dedicated and self contained facilities must be available for the production of particular medicinal products, such as highly sensitising materials (e.g. penicillins) or biological preparations (e.g. from live micro-organisms). The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.

- 3.7 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
- 3.8 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.
- 3.9 Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.
- 3.10 Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.
- 3.11 Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.
- 3.12 Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.
- 3.13 Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.
- 3.14 In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross-contamination and facilitate cleaning.
- 3.15 Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.
- 3.16 Production areas should be well lit, particularly where visual on-line controls are carried out.
- 3.17 In-process controls may be carried out within the production area provided they do not carry any risk for the production.

Storage Areas

- 3.18 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.
- 3.19 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

- 3.20 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.
- 3.21 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine should give equivalent security.
- 3.22 There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.
- 3.23 Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.
- 3.24 Highly active materials or products should be stored in safe and secure areas.
- 3.25 Printed packaging materials are considered critical to the conformity of the medicinal product and special attention should be paid to the safe and secure storage of these materials.

Quality Control Areas

- 3.26 Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, microbiologicals and radioisotopes, which should also be separated from each other.
- 3.27 Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.
- 3.28 Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.
- 3.29 Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

Ancillary Areas

- 3.30 Rest and refreshment rooms should be separate from other areas.
- 3.31 Facilities for changing clothes, and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.
- 3.32 Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.
- 3.33 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

Equipment

- 3.34 Manufacturing equipment should be designed, located and maintained to suit its intended purpose.
- 3.35 Repair and maintenance operations should not present any hazard to the quality of the products.
- 3.36 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.
- 3.37 Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.
- 3.38 Equipment should be installed in such a way as to prevent any risk of error or of contamination.
- 3.39 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.
- 3.40 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.
- 3.41 Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.
- 3.42 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.
- 3.43 Distilled, deionized and, where appropriate, other water pipes should be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.
- 3.44 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.



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EudraLex
The Rules Governing Medicinal Products in the European Union

Volume 4
Good Manufacturing Practice
Medicinal Products for Human and Veterinary Use

Chapter 4: Documentation

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 1

Reasons for changes: the sections on "generation and control of documentation" and "retention of documents" have been revised, in the light of the increasing use of electronic documents within the GMP environment.

Deadline for coming into operation: 30 June 2011

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Principle

Good documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements. The various types of documents and media used should be fully defined in the manufacturer's Quality Management System. Documentation may exist in a variety of forms, including paper-based, electronic or photographic media. The main objective of the system of documentation utilized must be to establish, control, monitor and record all activities which directly or indirectly impact on all aspects of the quality of medicinal products. The Quality Management System should include sufficient instructional detail to facilitate a common understanding of the requirements, in addition to providing for sufficient recording of the various processes and evaluation of any observations, so that ongoing application of the requirements may be demonstrated.

There are two primary types of documentation used to manage and record GMP compliance: instructions (directions, requirements) and records/reports. Appropriate good documentation practice should be applied with respect to the type of document.

Suitable controls should be implemented to ensure the accuracy, integrity, availability and legibility of documents. Instruction documents should be free from errors and available in writing. The term 'written' means recorded, or documented on media from which data may be rendered in a human readable form.

Required GMP documentation (by type):

Site Master File: A document describing the GMP related activities of the manufacturer.

Instructions (directions, or requirements) type:

Specifications Describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Manufacturing Formulae, Processing, Packaging and Testing Instructions: Provide detail all the starting materials, equipment and computerised systems (if any) to be used and specify all processing, packaging, sampling and testing instructions. In-process controls and process analytical technologies to be employed should be specified where relevant, together with acceptance criteria.

Procedures: (Otherwise known as Standard Operating Procedures, or SOPs), give directions for performing certain operations.

Protocols: Give instructions for performing and recording certain discreet operations.

Technical Agreements: Are agreed between contract givers and acceptors for outsourced activities.

Record/Report type:

Records: Provide evidence of various actions taken to demonstrate compliance with instructions, e.g. activities, events, investigations, and in the case of manufactured batches a history of each batch of product, including its distribution. Records include the raw data which is used to generate other records. For electronic records regulated users should define which data are to be used as raw data. At least, all data on which quality decisions are based should be defined as raw data

Certificates of Analysis: Provide a summary of testing results on samples of products or materials¹ together with the evaluation for compliance to a stated specification.

Reports: Document the conduct of particular exercises, projects or investigations, together with results, conclusions and recommendations.

Generation and Control of Documentation

4.1 All types of document should be defined and adhered to. The requirements apply equally to all forms of document media types. Complex systems need to be understood, well documented, validated, and adequate controls should be in place. Many documents (instructions and/or records) may exist in hybrid forms, i.e. some elements as electronic and others as paper based. Relationships and control measures for master documents, official copies, data handling and records need to be stated for both hybrid and homogenous systems. Appropriate controls for electronic documents such as templates, forms, and master documents should be implemented. Appropriate controls should be in place to ensure the integrity of the record throughout the retention period.

4.2 Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of Product Specification Files, Manufacturing and Marketing Authorisation dossiers, as appropriate. The reproduction of working documents from master documents should not allow any error to be introduced through the reproduction process.

4.3 Documents containing instructions should be approved, signed and dated by appropriate and authorised persons. Documents should have unambiguous contents and be uniquely identifiable. The effective date should be defined.

4.4 Documents containing instructions should be laid out in an orderly fashion and be easy to check. The style and language of documents should fit with their intended use. Standard Operating Procedures, Work Instructions and Methods should be written in an imperative mandatory style.

¹ Alternatively the certification may be based, in-whole or in-part, on the assessment of real time data (summaries and exception reports) from batch related process analytical technology (PAT), parameters or metrics as per the approved marketing authorisation dossier.

4.5 Documents within the Quality Management System should be regularly reviewed and kept up-to-date.

4.6 Documents should not be hand-written; although, where documents require the entry of data, sufficient space should be provided for such entries.

Good Documentation Practices

4.7 Handwritten entries should be made in clear, legible, indelible way.

4.8 Records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable.

4.9 Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

Retention of Documents

4.10 It should be clearly defined which record is related to each manufacturing activity and where this record is located. Secure controls must be in place to ensure the integrity of the record throughout the retention period and validated where appropriate.

4.11 Specific requirements apply to batch documentation which must be kept for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the Qualified Person, whichever is the longer. For investigational medicinal products, the batch documentation must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used. Other requirements for retention of documentation may be described in legislation in relation to specific types of product (e.g. Advanced Therapy Medicinal Products) and specify that longer retention periods be applied to certain documents.

4.12 For other types of documentation, the retention period will depend on the business activity which the documentation supports. Critical documentation, including raw data (for example relating to validation or stability), which supports information in the Marketing Authorisation should be retained whilst the authorization remains in force. It may be considered acceptable to retire certain documentation (e.g. raw data supporting validation reports or stability reports) where the data has been superseded by a full set of new data. Justification for this should be documented and should take into account the requirements for retention of batch documentation; for example, in the case of process validation data, the accompanying raw data should be retained for a period at least as long as the records for all batches whose release has been supported on the basis of that validation exercise.

The following section gives some examples of required documents. The quality management system should describe all documents required to ensure product quality and patient safety.

Specifications

4.13 There should be appropriately authorised and dated specifications for starting and packaging materials, and finished products.

Specifications for starting and packaging materials

4.14 Specifications for starting and primary or printed packaging materials should include or provide reference to, if applicable:

- a) A description of the materials, including:
 - The designated name and the internal code reference;
 - The reference, if any, to a pharmacopoeial monograph;
 - The approved suppliers and, if reasonable, the original producer of the material;
 - A specimen of printed materials;
- b) Directions for sampling and testing;
- c) Qualitative and quantitative requirements with acceptance limits;
- d) Storage conditions and precautions;
- e) The maximum period of storage before re-examination.

Specifications for intermediate and bulk products

4.15 Specifications for intermediate and bulk products should be available for critical steps or if these are purchased or dispatched. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

4.16 Specifications for finished products should include or provide reference to:

- a) The designated name of the product and the code reference where applicable;
- b) The formula;
- c) A description of the pharmaceutical form and package details;
- d) Directions for sampling and testing
- e) The qualitative and quantitative requirements, with the acceptance limits;
- f) The storage conditions and any special handling precautions, where applicable;
- g) The shelf-life.

Manufacturing Formula and Processing Instructions

Approved, written Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured.

4.17 The Manufacturing Formula should include:

- a) The name of the product, with a product reference code relating to its specification;
- b) A description of the pharmaceutical form, strength of the product and batch size;
- c) A list of all starting materials to be used, with the amount of each, described; mention should be made of any substance that may disappear in the course of processing;
- d) A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable

4.18 The Processing Instructions should include:

- a) A statement of the processing location and the principal equipment to be used;
- b) The methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);
- c) Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use;
- d) Detailed stepwise processing instructions [e.g. checks on materials, pre-treatments, sequence for adding materials, critical process parameters (time, temp etc)];
- e) The instructions for any in-process controls with their limits;
- f) Where necessary, the requirements for bulk storage of the products; including the container, labeling and special storage conditions where applicable;
- g) Any special precautions to be observed.

Packaging Instructions

4.19 Approved Packaging Instructions for each product, pack size and type should exist. These should include, or have a reference to, the following:

- a) Name of the product; including the batch number of bulk and finished product
- b) Description of its pharmaceutical form, and strength where applicable;
- c) The pack size expressed in terms of the number, weight or volume of the product in the final container;
- d) A complete list of all the packaging materials required, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
- e) Where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;
- f) Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations (line clearance), and that equipment is clean and suitable for use.
- g) Special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
- h) A description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- i) Details of in-process controls with instructions for sampling and acceptance limits.

Batch Processing Record

4.20 A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions, and should contain the following information:

- a) The name and batch number of the product;
- b) Dates and times of commencement, of significant intermediate stages and of completion of production;

- c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;
- d) The batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
- e) Any relevant processing operation or event and major equipment used;
- f) A record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
- g) The product yield obtained at different and pertinent stages of manufacture;
- h) Notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions;
- i) Approval by the person responsible for the processing operations.

Note: Where a validated process is continuously monitored and controlled, then automatically generated reports may be limited to compliance summaries and exception/ out-of-specification (OOS) data reports.

Batch Packaging Record

4.21 A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions.

The batch packaging record should contain the following information:

- a) The name and batch number of the product,
- b) The date(s) and times of the packaging operations;
- c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;
- d) Records of checks for identity and conformity with the packaging instructions, including the results of in-process controls;
- e) Details of the packaging operations carried out, including references to equipment and the packaging lines used;
- f) Whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;
- g) Notes on any special problems or unusual events including details, with signed authorisation for any deviation from the Packaging Instructions;
- h) The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation. Where there are robust electronic controls in place during packaging there may be justification for not including this information
- i) Approval by the person responsible for the packaging operations

Procedures and records

Receipt

4.22 There should be written procedures and records for the receipt of each delivery of each starting material, (including bulk, intermediate or finished goods), primary, secondary and printed packaging materials.

4.23 The records of the receipts should include:

- a) The name of the material on the delivery note and the containers;
- b) The "in-house" name and/or code of material (if different from a);
- c) Date of receipt;
- d) Supplier's name and, manufacturer's name;
- e) Manufacturer's batch or reference number;
- f) Total quantity and number of containers received;
- g) The batch number assigned after receipt;
- h) Any relevant comment.

4.24 There should be written procedures for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

Sampling

4.25 There should be written procedures for sampling, which include the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality.

Testing

4.26 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

Other

4.27 Written release and rejection procedures should be available for materials and products, and in particular for the certification for sale of the finished product by the Qualified Person(s). All records should be available to the Qualified Person. A system should be in place to indicate special observations and any changes to critical data.

4.28 Records should be maintained for the distribution of each batch of a product in order to facilitate recall of any batch, if necessary.

4.29 There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached, where appropriate, for the following examples:

- Validation and qualification of processes, equipment and systems;
- Equipment assembly and calibration;
- Technology transfer;
- Maintenance, cleaning and sanitation;

- Personnel matters including signature lists, training in GMP and technical matters, clothing and hygiene and verification of the effectiveness of training.
- Environmental monitoring;
- Pest control;
- Complaints;
- Recalls;
- Returns;
- Change control;
- Investigations into deviations and non-conformances;
- Internal quality/GMP compliance audits;
- Summaries of records where appropriate (e.g. product quality review);
- Supplier audits.

4.30 Clear operating procedures should be available for major items of manufacturing and test equipment.

4.31 Logbooks should be kept for major or critical analytical testing, production equipment, and areas where product has been processed. They should be used to record in chronological order, as appropriate, any use of the area, equipment/method, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.

4.32 An inventory of documents within the Quality Management System should be maintained.

CHAPTER 5 PRODUCTION

Principle

Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorisations.

General

- 5.1 Production should be performed and supervised by competent people.
- 5.2 All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.
- 5.3 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.
- 5.4 Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.
- 5.5 Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.
- 5.6 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.
- 5.7 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.
- 5.8 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
- 5.9 Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.
- 5.10 At every stage of processing, products and materials should be protected from microbial and other contamination.
- 5.11 When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitising materials.
- 5.12 At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and

batch number. Where applicable, this indication should also mention the stage of production.

- 5.13 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example, quarantined, accepted, rejected, clean, ...).
- 5.14 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.
- 5.15 Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.
- 5.16 Access to production premises should be restricted to authorised personnel.
- 5.17 Normally, the production of non-medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.

Prevention of cross-contamination in production

- 5.18 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Amongst the most hazardous contaminants are highly sensitising materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time.
- 5.19 Cross-contamination should be avoided by appropriate technical or organisational measures, for example:
 - a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;
 - b) providing appropriate air-locks and air extraction;
 - c) minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
 - d) keeping protective clothing inside areas where products with special risk of cross-contamination are processed;
 - e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
 - f) using "closed systems" of production;
 - g) testing for residues and use of cleaning status labels on equipment.
- 5.20 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.

Validation

- 5.21 Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.
- 5.22 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.
- 5.23 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated.
- 5.24 Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

Starting materials

- 5.25 The purchase of starting materials is an important operation which should involve staff who have a particular and thorough knowledge of the suppliers.
- 5.26 Starting materials should only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements, as well as complaints and rejection procedures are discussed with the manufacturer and the supplier.
- 5.27 For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.
- 5.28 If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.
- 5.29 Starting materials in the storage area should be appropriately labelled (see Chapter 5, item 13). Labels should bear at least the following information:
- the designated name of the product and the internal code reference where applicable;
 - a batch number given at receipt;
 - where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);
 - where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully computerised storage systems are used, all the above information need not necessarily be in a legible form on the label.

- 5.30 There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified (see Chapter 6, item 13).

- 5.31 Only starting materials which have been released by the Quality Control Department and which are within their shelf life should be used.
- 5.32 Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.
- 5.33 Each dispensed material and its weight or volume should be independently checked and the check recorded.
- 5.34 Materials dispensed for each batch should be kept together and conspicuously labelled as such.

Processing operations: intermediate and bulk products

- 5.35 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.
- 5.36 Intermediate and bulk products should be kept under appropriate conditions.
- 5.37 Critical processes should be validated (see "VALIDATION" in this Chapter).
- 5.38 Any necessary in-process controls and environmental controls should be carried out and recorded.
- 5.39 Any significant deviation from the expected yield should be recorded and investigated.

Packaging materials

- 5.40 The purchase, handling and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.
- 5.41 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorised access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorised personnel following an approved and documented procedure.
- 5.42 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.
- 5.43 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

Packaging operations

- 5.44 When setting up a programme for the packaging operations, particular attention should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

- 5.45 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate check-list.
- 5.46 The name and batch number of the product being handled should be displayed at each packaging station or line.
- 5.47 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.
- 5.48 Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.
- 5.49 Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.
- 5.50 The correct performance of any printing operation (for example code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be re-checked at regular intervals.
- 5.51 Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.
- 5.52 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.
- 5.53 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.
- 5.54 On-line control of the product during packaging should include at least checking the following:
- a) general appearance of the packages;
 - b) whether the packages are complete;
 - c) whether the correct products and packaging materials are used;
 - d) whether any over-printing is correct;
 - e) correct functioning of line monitors.
- Samples taken away from the packaging line should not be returned.
- 5.55 Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed record should be kept of this operation.
- 5.56 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.
- 5.57 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

Finished products

- 5.58 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.
- 5.59 The evaluation of finished products and documentation which is necessary before release of product for sale are described in Chapter 6 (Quality Control).
- 5.60 After release, finished products should be stored as usable stock under conditions established by the manufacturer.

Rejected, recovered and returned materials

- 5.61 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorised personnel.
- 5.62 The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. Record should be kept of the reprocessing.
- 5.63 The recovery of all or part of earlier batches which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorised beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.
- 5.64 The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.
- 5.65 Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for re-sale, re-labelling or recovery in a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical re-processing to recover active ingredient may be possible. Any action taken should be appropriately recorded.



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Consumer goods
Pharmaceuticals

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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

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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.



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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

Chapter 7

Outsourced Activities

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 1

Reasons for changes: In view of the ICH Q10 guideline on the Pharmaceutical Quality System, Chapter 7 of the GMP Guide has been revised in order to provide updated guidance on outsourced GMP regulated activities beyond the current scope of contract manufacture and analysis operations. The title of the Chapter has been changed to reflect this.

Deadline for coming into operation: 31 January 2013

Principle

Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality. There must be a written Contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party. The Quality Management System of the Contract Giver must clearly state the way that the Qualified Person certifying each batch of product for release exercises his full responsibility.

Note: This Chapter deals with the responsibilities of manufacturers towards the Competent Authorities of the Member States with respect to the granting of marketing and manufacturing authorizations. It is not intended in any way to affect the respective liability of Contract Acceptors and Contract Givers to consumers; this is governed by other provisions of Community and national law.

General

7.1 There should be a written Contract covering the outsourced activities, the products or operations to which they are related, and any technical arrangements made in connection with it.

7.2 All arrangements for the outsourced activities including any proposed changes in technical or other arrangements should be in accordance with regulations in force, and the Marketing Authorisation for the product concerned, where applicable.

7.3 Where the marketing authorization holder and the manufacturer are not the same, appropriate arrangements should be in place, taking into account the principles described in this chapter.

The Contract Giver

7.4 The pharmaceutical quality system of the Contract Giver should include the control and review of any outsourced activities. The Contract Giver is ultimately responsible to ensure processes are in place to assure the control of outsourced activities. These processes should incorporate quality risk management principles and notably include:

7.5 Prior to outsourcing activities, the Contract Giver is responsible for assessing the legality, suitability and the competence of the Contract Acceptor to carry out successfully the outsourced activities. The Contract Giver is also responsible for ensuring by means of the Contract that the principles and guidelines of GMP as interpreted in this Guide are followed.

7.6 The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly in accordance with regulations in force, and the Marketing Authorisation for the product concerned. The Contract Giver should ensure that the Contract Acceptor is

fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products.

7.7 The Contract Giver should monitor and review the performance of the Contract Acceptor and the identification and implementation of any needed improvement.

7.8 The Contract Giver should be responsible for reviewing and assessing the records and the results related to the outsourced activities. He should also ensure, either by himself, or based on the confirmation of the Contract Acceptor's Qualified Person, that all products and materials delivered to him by the Contract Acceptor have been processed in accordance with GMP and the marketing authorisation.

The Contract Acceptor

7.9 The Contract Acceptor must be able to carry out satisfactorily the work ordered by the Contract Giver such as having adequate premises, equipment, knowledge, experience, and competent personnel.

7.10 The Contract Acceptor should ensure that all products, materials and knowledge delivered to him are suitable for their intended purpose.

7.11 The Contract Acceptor should not subcontract to a third party any of the work entrusted to him under the Contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that information and knowledge, including those from assessments of the suitability of the third party, are made available in the same way as between the original Contract Giver and Contract Acceptor.

7.12 The Contract Acceptor should not make unauthorized changes, outside the terms of the Contract, which may adversely affect the quality of the outsourced activities for the Contract Giver.

7.13 The Contract Acceptor should understand that outsourced activities, including contract analysis, may be subject to inspection by the competent authorities.

The Contract

7.14 A Contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities and communication processes relating to the outsourced activities. Technical aspects of the Contract should be drawn up by competent persons suitably knowledgeable in related outsourced activities and Good Manufacturing Practice. All arrangements for outsourced activities must be in accordance with regulations in force and the Marketing Authorisation for the product concerned and agreed by both parties.

7.15 The Contract should describe clearly who undertakes each step of the outsourced activity, e.g. knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials,

undertaking production and quality controls (including in-process controls, sampling and analysis).

7.16 All records related to the outsourced activities, e.g. manufacturing, analytical and distribution records, and reference samples, should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect or to investigating in the case of a suspected falsified product must be accessible and specified in the relevant procedures of the Contract Giver.

7.17 The Contract should permit the Contract Giver to audit outsourced activities, performed by the Contract Acceptor or his mutually agreed subcontractors



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Part I
Chapter 8 Complaints and Product Recall

Document History	
Revision to include new Points 8.7 on requirements on counterfeit products and transferring the original Points 8.7 into a modified Point 8.8; slight modification of Point 8.16	December 2005
Date of revised version coming into operation	01 February 2006

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Principle Complaints Recalls

Principle

All complaints and other information concerning potentially defective products must be reviewed carefully according to written procedures. In order to provide for all contingencies, and in accordance with Article 117 of Directive 2001/83/EC and Article 84 of Directive 2001/82/EC, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

Complaints

- 8.1 A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him. If this person is not the Qualified Person, the latter should be made aware of any complaint, investigation or recall.
- 8.2 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.
- 8.3 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control should normally be involved in the study of such problems.
- 8.4 If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches in order to determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch should be investigated.
- 8.5 All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
- 8.6 Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.
- 8.7 Special attention should be given to establishing whether a complaint was caused because of counterfeiting.
- 8.8 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, detection of counterfeiting or any other serious quality problems with a product

Recalls

- 8.9 A person should be designated as responsible for execution and co-ordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organisation. If this person is not the Qualified Person, the latter should be made aware of any recall operation.
- 8.10 There should be established written procedures, regularly checked and updated when necessary, in order to organise any recall activity.

- 8.11 Recall operations should be capable of being initiated promptly and at any time.
- 8.12 All Competent Authorities of all countries to which products may have been distributed should be informed promptly if products are intended to be recalled because they are, or are suspected of being defective.
- 8.13 The distribution records should be readily available to the person(s) responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples.
- 8.14 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.
- 8.15 The progress of the recall process should be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the products.
- 8.16 The effectiveness of the arrangements for recalls should be evaluated regularly.

CHAPTER 9 SELF INSPECTION

Principle

Self inspections should be conducted in order to monitor the implementation and compliance with Good Manufacturing Practice principles and to propose necessary corrective measures.

- 9.1 Personnel matters, premises, equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self inspection, should be examined at intervals following a pre-arranged programme in order to verify their conformity with the principles of Quality Assurance.
- 9.2 Self inspections should be conducted in an independent and detailed way by designated competent person(s) from the company. Independent audits by external experts may also be useful.
- 9.3 All self inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.



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The Rules Governing Medicinal Products in the European Union Volume 4

Good Manufacturing Practice

Medicinal Products for Human and Veterinary Use

Part II: Basic Requirements for Active Substances used as Starting Materials

Document History	
An amendment is made to Part II of the GMP Guide to incorporate principles of Quality Risk Management in line with the ICH Q9 guideline on Quality Risk Management. Amendments correspond to similar changes made to Part I Chapter 1 of the Guide and published in February 2008. A new section on Quality Risk Management is introduced as section 2.19. The remaining sections of chapter 2 are renumbered. A minor change is made to section 2.21. No other changes have been made.	September 2007
Public consultation	April 2008 until October 2008
Adopted by the European Commission	31 January 2010
Deadline for coming into operation	31 July 2010

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1 Introduction

This guideline was published in November 2000 as Annex 18 to the GMP Guide reflecting the EU's agreement to ICH Q7A and has been used by manufacturers and GMP inspectorates on a voluntary basis. Article 46 (f) of Directive 2001/83/EC and Article 50 (f) of Directive 2001/82/EC; as amended by Directives 2004/27/EC and 2004/28/EC respectively, place new obligations on manufacturing authorisation holders to use only active substances that have been manufactured in accordance with Good Manufacturing Practice for starting materials. The directives go on to say that the principles of Good Manufacturing Practice for active substances are to be adopted as detailed guidelines. Member States have agreed that the text of former Annex 18 should form the basis of the detailed guidelines to create Part II of the GMP Guide.

1.1 Objective

These guidelines are intended to provide guidance regarding Good Manufacturing Practice (GMP) for the manufacture of active substances under an appropriate system for managing quality. It is also intended to help ensure that active substances meet the requirements for quality and purity that they purport or are represented to possess.

In these guidelines "manufacturing" includes all operations of receipt of materials, production, packaging, repackaging, labeling, relabelling, quality control, release, storage and distribution of active substances and the related controls. The term "should" indicates recommendations that are expected to apply unless shown to be inapplicable, modified in any relevant annexes to the GMP Guide, or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance.

The GMP Guide as a whole does not cover safety aspects for the personnel engaged in manufacture, nor aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by other parts of the legislation.

These guidelines are not intended to define registration requirements or modify pharmacopoeial requirements and do not affect the ability of the responsible competent authority to establish specific registration requirements regarding active substances within the context of marketing/manufacturing authorisations. All commitments in registration documents must be met.

1.2 Scope

These guidelines apply to the manufacture of active substances for medicinal products for both human and veterinary use. They apply to the manufacture of sterile active substances only up to the point immediately prior to the active substance being rendered sterile. The sterilisation and aseptic processing of sterile active substances are not covered, but should be performed in accordance with the principles and guidelines of GMP as laid down in Directive 2003/94/EC and interpreted in the GMP Guide including its Annex 1.

In the case of ectoparasiticides for veterinary use, other standards than these guidelines, that ensure that the material is of appropriate quality, may be used.

These guidelines exclude, whole blood and plasma, as Directive 2002/98/EC and the technical requirements supporting that directive lay down the detailed requirements for the collection and testing of blood, however, it does include active substances that are produced using blood or plasma as raw materials. Finally, these guidelines do not apply

to bulk-packaged medicinal products. They apply to all other active starting materials subject to any derogations described in the annexes to the GMP Guide, in particular Annexes 2 to 7 where supplementary guidance for certain types of active substance may be found. The annexes will consequently undergo a review but in the meantime and only until this review is complete, manufacturers may choose to continue to use Part I of the basic requirements and the relevant annexes for products covered by those annexes, or may already apply Part II.

Section 19 contains guidance that only applies to the manufacture of active substances used in the production of investigational medicinal products although it should be noted that its application in this case, although recommended, is not required by Community legislation.

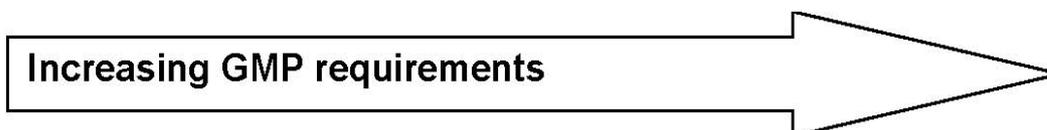
An “Active Substance Starting Material” is a raw material, intermediate, or an active substance that is used in the production of an active substance and that is incorporated as a significant structural fragment into the structure of the active substance. An Active Substance Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. Active Substance Starting Materials normally have defined chemical properties and structure.

The manufacturer should designate and document the rationale for the point at which production of the active substance begins. For synthetic processes, this is known as the point at which "Active Substance Starting Materials" are entered into the process. For other processes (e.g. fermentation, extraction, purification, etc), this rationale should be established on a case-by-case basis. Table 1 gives guidance on the point at which the Active Substance Starting Material is normally introduced into the process. From this point on, appropriate GMP as defined in these guidelines should be applied to these intermediate and/or active substance manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the active substance. However, it should be noted that the fact that a manufacturer chooses to validate a process step does not necessarily define that step as critical. The guidance in this document would normally be applied to the steps shown in grey in Table 1. It does not imply that all steps shown should be completed. The stringency of GMP in active substance manufacturing should increase as the process proceeds from early steps to final steps, purification, and packaging. Physical processing of active substances, such as granulation, coating or physical manipulation of particle size (e.g. milling, micronising), should be conducted at least to the standards of these guidelines. These guidelines do not apply to steps prior to the first introduction of the defined "Active Substance Starting Material".

In the remainder of this guideline the term Active Pharmaceutical Ingredient (API) is used repeatedly and should be considered interchangeable with the term “Active Substance”. The glossary in section 20 of Part II should only be applied in the context of Part II. Some of the same terms are already defined in Part I of the GMP guide and these therefore should only be applied in the context of Part I.

Table 1: Application of this Guide to API Manufacturing

Type of Manufacturing	Application of this Guide to steps (shown in grey) used in this type of manufacturing				
Chemical Manufacturing	Production of the API Starting Material	Introduction of the API Starting Material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API Starting Material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/ comminuting			Physical processing, and packaging
Biotechnology : fermentation/ cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
“Classical” Fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging



2 Quality Management

2.1 Principles

2.10 Quality should be the responsibility of all persons involved in manufacturing.

2.11 Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

2.12 The system for managing quality should encompass the organisational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality related activities should be defined and documented.

2.13 There should be a quality unit(s) that is independent of production and that fulfills both quality assurance (*QA*) and quality control (*QC*) responsibilities. This 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.

2.14 The persons authorised to release intermediates and APIs should be specified.

2.15 All quality related activities should be recorded at the time they are performed.

2.16 Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.

2.17 No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine as described in Section 10.20 or the use of raw materials or intermediates pending completion of evaluation).

2.18 Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects and related actions (e.g. quality related complaints, recalls, regulatory actions, etc.).

2.19 To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented quality system incorporating Good Manufacturing Practice, Quality Control and Quality Risk Management.

2.2 Quality Risk Management

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

2.21 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 through communication with the user of the active substance
- 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.

2.3 Responsibilities of the Quality Unit(s)

2.30 The quality unit(s) should be involved in all quality-related matters.

2.31 The quality unit(s) should review and approve all appropriate quality-related documents.

2.32 The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include but not necessarily be limited to:

1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company;
2. Establishing a system to release or reject raw materials, intermediates, packaging and labelling materials;
3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution;
4. Making sure that critical deviations are investigated and resolved;
5. Approving all specifications and master production instructions;
6. Approving all procedures impacting the quality of intermediates or APIs;
7. Making sure that internal audits (self-inspections) are performed;
8. Approving intermediate and API contract manufacturers;
9. Approving changes that potentially impact intermediate or API quality;
10. Reviewing and approving validation protocols and reports;
11. Making sure that quality related complaints are investigated and resolved;
12. Making sure that effective systems are used for maintaining and calibrating critical equipment;
13. Making sure that materials are appropriately tested and the results are reported;
14. Making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate; and
15. Performing product quality reviews (as defined in Section 2.5)

2.4 Responsibility for Production Activities

The responsibility for production activities should be described in writing, and should include but not necessarily be limited to:

1. Preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures;
2. Producing APIs and, when appropriate, intermediates according to pre-approved instructions;
3. Reviewing all production batch records and ensuring that these are completed and signed;
4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded;

5. Making sure that production facilities are clean and when appropriate disinfected;
6. Making sure that the necessary calibrations are performed and records kept;
7. Making sure that the premises and equipment are maintained and records kept;
8. Making sure that validation protocols and reports are reviewed and approved;
9. Evaluating proposed changes in product, process or equipment; and
10. Making sure that new and, when appropriate, modified facilities and equipment are qualified.

2.5 Internal Audits (Self Inspection)

2.50 In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.

2.51 Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

2.6 Product Quality Review

2.60 Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least:

- A review of critical in-process control and critical API test results;
- A review of all batches that failed to meet established specification(s);
- A review of all critical deviations or non-conformances and related investigations;
- A review of any changes carried out to the processes or analytical methods;
- A review of results of the stability monitoring program;
- A review of all quality-related returns, complaints and recalls; and
- A review of adequacy of corrective actions.

2.61 The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

3 Personnel

3.1 Personnel Qualifications

3.10 There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.

3.11 The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.

3.12 Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates

to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

3.2 Personnel Hygiene

3.20 Personnel should practice good sanitation and health habits.

3.21 Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn when necessary, to protect intermediates and APIs from contamination.

3.22 Personnel should avoid direct contact with intermediates or APIs.

3.23 Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

3.24 Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

3.3 Consultants

3.30 Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

3.31 Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

4 Buildings and Facilities

4.1 Design and Construction

4.10 Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.

4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

4.12 Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

4.13 The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

4.14 There should be defined areas or other control systems for the following

activities:

- Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection;
- Quarantine before release or rejection of intermediates and APIs;
- Sampling of intermediates and APIs;
- Holding rejected materials before further disposition (e.g., return, reprocessing or destruction)
- Storage of released materials;
- Production operations;
- Packaging and labelling operations; and
- Laboratory operations.

4.15 Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

4.16 Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.

4.2 Utilities

4.20 All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.

4.21 Adequate ventilation, air filtration and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimise risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

4.22 If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.

4.23 Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.

4.24 Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

4.3 Water

4.30 Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.

4.31 Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.

4.32 If drinking (potable) water is insufficient to assure API quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established.

4.33 Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.

4.34 Where the manufacturer of a non-sterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

4.4 Containment

4.40 Dedicated production areas, which can include facilities, air handling equipment and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.

4.41 Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

4.42 Appropriate measures should be established and implemented to prevent cross-contamination from personnel, materials, etc. moving from one dedicated area to another.

4.43 Any production activities (including weighing, milling, or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic non-pharmaceutical materials should be separate from APIs.

4.5 Lighting

4.50 Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

4.6 Sewage and Refuse

4.60 Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

4.7 Sanitation and Maintenance

4.70 Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

4.71 Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.

4.72 When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labelling materials, intermediates, and APIs.

5 Process Equipment

5.1 Design and Construction

5.10 Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.

5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

5.12 Production equipment should only be used within its qualified operating range.

5.13 Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids or coolants, should not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food grade lubricants and oils should be used.

5.15 Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

5.16 A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

5.2 Equipment Maintenance and Cleaning

5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.

5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include:

- Assignment of responsibility for cleaning of equipment;
- Cleaning schedules, including, where appropriate, sanitizing schedules;

- A complete description of the methods and materials, including dilution of cleaning agents used to clean equipment;
- When appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;
- Instructions for the removal or obliteration of previous batch identification;
- Instructions for the protection of clean equipment from contamination prior to use;
- Inspection of equipment for cleanliness immediately before use, if practical; and
- Establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.

5.22 Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carry-over of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent build-up and carry-over of contaminants (e.g. degradants or objectionable levels of micro-organisms).

5.24 Non-dedicated equipment should be cleaned between production of different materials to prevent cross-contamination.

5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

5.26 Equipment should be identified as to its contents and its cleanliness status by appropriate means.

5.3 Calibration

5.30 Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

5.31 Equipment calibrations should be performed using standards traceable to certified standards, if existing.

5.32 Records of these calibrations should be maintained.

5.33 The current calibration status of critical equipment should be known and verifiable.

5.34 Instruments that do not meet calibration criteria should not be used.

5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

5.4 Computerized Systems

5.40 GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.

5.41 Appropriate installation qualification and operational qualification should

demonstrate the suitability of computer hardware and software to perform assigned tasks.

5.42 Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.

5.43 Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g. system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.

5.44 Written procedures should be available for the operation and maintenance of computerized systems.

5.45 Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.

5.46 Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

5.47 Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.

5.48 If system breakdowns or failures would result in the permanent loss of records, a back-up system should be provided. A means of ensuring data protection should be established for all computerized systems.

5.49 Data can be recorded by a second means in addition to the computer system.

6 Documentation and Records

6.1 Documentation System and Specifications

6.10 All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved and distributed according to written procedures. Such documents can be in paper or electronic form.

6.11 The issuance, revision, superseding and withdrawal of all documents should be controlled with maintenance of revision histories.

6.12 A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.

6.13 All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

6.14 When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still readable.

6.15 During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

6.16 Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

6.17 Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labelling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.

6.18 If electronic signatures are used on documents, they should be authenticated and secure.

6.2 Equipment Cleaning and Use Record

6.20 Records of major equipment use, cleaning, sanitization and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

6.21 If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

6.3 Records of Raw Materials, Intermediates, API Labelling and Packaging Materials

6.30 Records should be maintained including:

- The name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates or labelling and packaging materials for APIs; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt;
- The results of any test or examination performed and the conclusions derived from this;
- Records tracing the use of materials;
- Documentation of the examination and review of API labelling and packaging materials for conformity with established specifications; and

-The final decision regarding rejected raw materials, intermediates or API labeling and packaging materials.

6.31 Master (approved) labels should be maintained for comparison to issued labels.

6.4 Master Production Instructions (Master Production and Control Records)

6.40 To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).

6.41 Master production instructions should include:

- The name of the intermediate or API being manufactured and an identifying document reference code, if applicable;
- A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;
- An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included where they are justified;
- The production location and major production equipment to be used;
- Detailed production instructions, including the:
 - sequences to be followed,
 - ranges of process parameters to be used,
- sampling instructions and in-process controls with their acceptance criteria, where appropriate,
- time limits for completion of individual processing steps and/or the total process, where appropriate; and
- expected yield ranges at appropriate phases of processing or time;
- Where appropriate, special notations and precautions to be followed, or cross references to these; and
- The instructions for storage of the intermediate or API to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

6.5 Batch Production Records (Batch Production and Control Records)

6.50 Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

6.51 These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.

6.52 Documentation of completion of each significant step in the batch production records (batch production and control records) should include:

- Dates and, when appropriate, times;
- Identity of major equipment (e.g., reactors, driers, mills, etc.) used;

- Specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing;
- Actual results recorded for critical process parameters;
- Any sampling performed;
- Signatures of the persons performing and directly supervising or checking each critical step in the operation;
- In-process and laboratory test results;
- Actual yield at appropriate phases or times;
- Description of packaging and label for intermediate or API;
- Representative label of API or intermediate if made commercially available;
- Any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately; and
- Results of release testing.

6.53 Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

6.6 Laboratory Control Records

6.60 Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing;
- A statement of or reference to each test method used;
- A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents and standard solutions,
- A complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested;
- A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors;
- A statement of the test results and how they compare with established acceptance criteria;
- The signature of the person who performed each test and the date(s) the tests were performed; and
- The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

6.61 Complete records should also be maintained for:

- Any modifications to an established analytical method,
- Periodic calibration of laboratory instruments, apparatus, gauges, and recording devices;
- All stability testing performed on APIs; and
- Out-of-specification (OOS) investigations.

6.7 Batch Production Record Review

6.70 Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labelling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

6.71 Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of non-critical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).

6.72 All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

6.73 The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

7 Materials Management

7.1 General Controls

7.10 There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.

7.11 Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.

7.12 Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s).

7.13 If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.

7.14 Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control.

7.2 Receipt and Quarantine

7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labelling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined or tested as appropriate, and released for use.

7.21 Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.

7.22 If bulk deliveries are made in non-dedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:

- certificate of cleaning
- testing for trace impurities
- audit of the supplier.

7.23 Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.

7.24 Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

7.3 Sampling and Testing of Incoming Production Materials

7.30 At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below in 7.32. A supplier's Certificate of Analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

7.31 Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals.

7.32 Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's Certificate of Analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.

7.33 Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.

7.34 Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

7.35 Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

7.4 Storage

7.40 Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

7.41 Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.

7.42 Materials should be stored under conditions and for a period that have no adverse

affect on their quality, and should normally be controlled so that the oldest stock is used first.

7.43 Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

7.44 Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorised use in manufacturing.

7.5 Re-evaluation

7.50 Materials should be re-evaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

8 Production and In-Process Controls

8.1 Production Operations

8.10 Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

8.11 If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

- Material name and/or item code;
- Receiving or control number;
- Weight or measure of material in the new container; and
- Re-evaluation or retest date if appropriate.

8.12 Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

8.13 Other critical activities should be witnessed or subjected to an equivalent control.

8.14 Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.

8.15 Any deviation should be documented and explained. Any critical deviation should be investigated.

8.16 The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.

8.17 Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

8.2 Time Limits

8.20 If time limits are specified in the master production instruction (see 6.41), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.

8.21 Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

8.3 In-process Sampling and Controls

8.30 Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.

8.31 The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).

8.32 Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).

8.33 In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made within pre-established limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.

8.34 Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.

8.35 In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.

8.36 Out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

8.4 Blending Batches of Intermediates or APIs

8.40 For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g., collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

8.41 Out-Of-Specification batches should not be blended with other batches for the

purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

8.42 Acceptable blending operations include but are not limited to:

- Blending of small batches to increase batch size

- Blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch.

8.43 Blending processes should be adequately controlled and documented and the blended batch should be tested for conformance to established specifications where appropriate.

8.44 The batch record of the blending process should allow traceability back to the individual batches that make up the blend.

8.45 Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle size distribution, bulk density, and tap density) that may be affected by the blending process.

8.46 If the blending could adversely affect stability, stability testing of the final blended batches should be performed.

8.47 The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

8.5 Contamination Control

8.50 Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of degradants or microbial contamination that may adversely alter the established API impurity profile.

8.51 Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.

8.52 Precautions to avoid contamination should be taken when APIs are handled after purification.

9 Packaging and Identification Labelling of APIs and Intermediates

9.1 General

9.10 There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labelling materials.

9.11 Packaging and labelling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.

9.12 Records should be maintained for each shipment of labels and packaging

materials showing receipt, examination, or testing, and whether accepted or rejected.

9.2 Packaging Materials

9.20 Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

9.21 Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.

9.22 If containers are re-used, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.

9.3 Label Issuance and Control

9.30 Access to the label storage areas should be limited to authorised personnel.

9.31 Procedures should be used to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labelled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).

9.32 All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.

9.33 Obsolete and out-dated labels should be destroyed.

9.34 Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

9.35 Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.

9.36 A printed label representative of those used should be included in the batch production record.

9.4 Packaging and Labelling Operations

9.40 There should be documented procedures designed to ensure that correct packaging materials and labels are used.

9.41 Labelling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or APIs.

9.42 Labels used on containers of intermediates or APIs should indicate the name or identifying code, the batch number of the product, and storage conditions, when such information is critical to assure the quality of intermediate or API.

9.43 If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, and special transport conditions and any special legal requirements

should also be included on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.

9.44 Packaging and labelling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log, or other documentation system.

9.45 Packaged and labelled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.

9.46 Intermediate or API containers that are transported outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

10 Storage and Distribution

10.1 Warehousing Procedures

10.10 Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.

10.11 Unless there is an alternative system to prevent the unintentional or unauthorised use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.

10.2 Distribution Procedures

10.20 APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.

10.21 APIs and intermediates should be transported in a manner that does not adversely affect their quality.

10.22 Special transport or storage conditions for an API or intermediate should be stated on the label.

10.23 The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

10.24 A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

11 Laboratory Controls

11.1 General Controls

11.10 The independent quality unit(s) should have at its disposal adequate laboratory facilities.

11.11 There should be documented procedures describing sampling, testing, approval or rejection of materials, and recording and storage of laboratory data. Laboratory records should be maintained in accordance with Section 6.6.

11.12 All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).

11.13 Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.

11.14 Laboratory controls should be followed and documented at the time of performance. Any departures from the above described procedures should be documented and explained.

11.15 Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any re-sampling and/or retesting after OOS results should be performed according to a documented procedure.

11.16 Reagents and standard solutions should be prepared and labelled following written procedures. "Use by" dates should be applied as appropriate for analytical reagents or standard solutions.

11.17 Primary reference standards should be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognised source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

11.18 Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

11.19 Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

11.2 Testing of Intermediates and APIs

11.20 For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.

11.21 An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed, and classification of each identified impurity (e.g. inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin. Biotechnology considerations are covered in ICH Guideline Q6B.

11.22 The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data in order to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.

11.23 Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.

11.3 Validation of Analytical Procedures - see Section 12.

11.4 Certificates of Analysis

11.40 Authentic Certificates of Analysis should be issued for each batch of intermediate or API on request.

11.41 Information on the name of the intermediate or API including where appropriate its grade, the batch number, and the date of release should be provided on the Certificate of Analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.

11.42 The Certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).

11.43 Certificates should be dated and signed by authorised personnel of the quality unit(s) and should show the name, address and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the Certificate of Analysis should show the name, address and telephone number of the repacker/ reprocessor and a reference to the name of the original manufacturer.

11.44 If new Certificates are issued by or on behalf of repackers/ reprocessors, agents or brokers, these Certificates should show the name, address and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch Certificate, a copy of which should be attached.

11.5 Stability Monitoring of APIs

11.50 A documented, on-going testing program should be designed to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.

11.51 The test procedures used in stability testing should be validated and be stability indicating.

11.52 Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.

11.53 Normally the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least two years, fewer than three batches can be used.

11.54 Thereafter, at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.

11.55 For APIs with short shelf-lives, testing should be done more frequently. For example, for those biotechnological/biologic and other APIs with shelf-lives of one year or less, stability samples should be obtained and should be tested monthly for the first three months, and at three month intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g. 9 month testing) can be considered.

11.56 Where appropriate, the stability storage conditions should be consistent with the ICH guidelines on stability.

11.6 Expiry and Retest Dating

11.60 When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g. published data, test results).

11.61 An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.

11.62 Preliminary API expiry or retest dates can be based on pilot scale batches if

(1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale; and (2) the quality of the API represents the material to be made on a commercial scale.

11.63 A representative sample should be taken for the purpose of performing a retest.

11.7 Reserve/Retention Samples

11.70 The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.

11.71 Appropriately identified reserve samples of each API batch should be retained for one year after the expiry date of the batch assigned by the manufacturer, or for three years after distribution of the batch, whichever is the longer. For APIs with retest dates, similar reserve samples should be retained for three years after the batch is completely distributed by the manufacturer.

11.72 The reserve sample should be stored in the same packaging system in which the

API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

12 Validation

12.1 Validation Policy

12.10 The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval and documentation of each validation phase, should be documented.

12.11 The critical parameters/attributes should normally be identified during the development stage or from historical data, and the ranges necessary for the reproducible operation should be defined. This should include:

- Defining the API in terms of its critical product attributes;
- Identifying process parameters that could affect the critical quality attributes of the API;
- Determining the range for each critical process parameter expected to be used during routine manufacturing and process control.

12.12 Validation should extend to those operations determined to be critical to the quality and purity of the API.

12.2 Validation Documentation

12.20 A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.

12.21 The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective, concurrent) and the number of process runs.

12.22 A validation report that cross-references the validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

12.23 Any variations from the validation protocol should be documented with appropriate justification.

12.3 Qualification

12.30 Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

- Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.
- Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements.
- Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.
- Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

12.4 Approaches to Process Validation

12.40 Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

12.41 There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These approaches and their applicability are listed below.

12.42 Prospective validation should normally be performed for all API processes as defined in 12.12. Prospective validation performed on an API process should be completed before the commercial distribution of the final drug product manufactured from that API.

12.43 Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the API batches.

12.44 An exception can be made for retrospective validation for well established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where:

- (1) Critical quality attributes and critical process parameters have been identified;
- (2) Appropriate in-process acceptance criteria and controls have been established;
- (3) There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability; and,
- (4) Impurity profiles have been established for the existing API.

12.45 Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

12.5 Process Validation Program

12.50 The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.

12.51 Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.

12.52 Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to or better than historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

12.6 Periodic Review of Validated Systems

12.60 Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

12.7 Cleaning Validation

12.70 Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.

12.71 Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.

12.72 The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labelled.

12.73 Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when

product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).

12.74 Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable, verifiable and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component.

12.75 Equipment cleaning/sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., non-sterile APIs used to manufacture sterile products).

12.76 Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.

12.8 Validation of Analytical Methods

12.80 Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognised standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.

12.81 Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.

12.82 Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.

12.83 Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

13 Change Control

13.10 A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.

13.11 Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware),

processing steps, labelling and packaging materials, and computer software.

13.12 Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organisational units, and reviewed and approved by the quality unit(s).

13.13 The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process.

13.14 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

13.15 After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.

13.16 The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.

13.17 Current dosage form manufacturers should be notified of changes from established production and process control procedures that can impact the quality of the API.

14 Rejection and Re-Use of Materials

14.1 Rejection

14.10 Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.

14.2 Reprocessing

14.20 Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.

14.21 Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.

14.22 Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely impacted due to the potential formation of by-

products and over-reacted materials.

14.3 Reworking

14.30 Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for non-conformance should be performed.

14.31 Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.

14.32 Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

14.4 Recovery of Materials and Solvents

14.40 Recovery (e.g. from mother liquor or filtrates) of reactants, intermediates, or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

14.41 Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or co-mingling with other approved materials.

14.42 Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

14.43 The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

14.5 Returns

14.50 Returned intermediates or APIs should be identified as such and quarantined.

14.51 If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked, or destroyed, as appropriate.

14.52 Records of returned intermediates or APIs should be maintained. For each return, documentation should include:

- Name and address of the consignee
- Intermediate or API, batch number, and quantity returned
- Reason for return
- Use or disposal of the returned intermediate or API

15 Complaints and Recalls

15.10 All quality related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

15.11 Complaint records should include:

- Name and address of complainant;
- Name (and, where appropriate, title) and phone number of person submitting the complaint;
- Complaint nature (including name and batch number of the API);
- Date complaint is received;
- Action initially taken (including dates and identity of person taking the action);
- Any follow-up action taken;
- Response provided to the originator of complaint (including date response sent);and
- Final decision on intermediate or API batch or lot.

15.12 Records of complaints should be retained in order to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.

15.13 There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.

15.14 The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.

15.15 In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.

16 Contract Manufacturers (including Laboratories)

16.10 All contract manufacturers (including laboratories) should comply with the GMP defined in this Guide. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

16.11 Contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations occurring at the contract sites.

16.12 There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.

16.13 The contract should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.

16.14 Where subcontracting is allowed, the contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements.

16.15 Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.

16.16 Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

17 Agents, Brokers, Traders, Distributors, Repackers, and Relabellers

17.1 Applicability

17.10 This section applies to any party other than the original manufacturer who may trade and/or take possession, repack, relabel, manipulate, distribute or store an API or intermediate.

17.11 All agents, brokers, traders, distributors, repackers, and relabellers should comply with GMP as defined in this Guide.

17.2 Traceability of Distributed APIs and Intermediates

17.20 Agents, brokers, traders, distributors, repackers, or relabellers should maintain complete traceability of APIs and intermediates that they distribute. Documents that should be retained and available include:

- Identity of original manufacturer
- Address of original manufacturer
- Purchase orders
- Bills of lading (transportation documentation)
- Receipt documents
- Name or designation of API or intermediate
- Manufacturer's batch number
- Transportation and distribution records
- All authentic Certificates of Analysis, including those of the original manufacturer
- Retest or expiry date

17.3 Quality Management

17.30 Agents, brokers, traders, distributors, repackers, or relabellers should establish, document and implement an effective system of managing quality, as specified in Section 2.

17.4 Repackaging, Relabelling and Holding of APIs and Intermediates

17.40 Repackaging, relabelling and holding of APIs and intermediates should be performed under appropriate GMP controls, as stipulated in this Guide, to avoid mix-ups and loss of API or intermediate identity or purity.

17.41 Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

17.5 Stability

17.50 Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the API or intermediate manufacturer.

17.6 Transfer of Information

17.60 Agents, brokers, distributors, repackers, or relabellers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer.

17.61 The agent, broker, trader, distributor, repacker, or relabeller who supplies the API or intermediate to the customer should provide the name of the original API or intermediate manufacturer and the batch number(s) supplied.

17.62 The agent should also provide the identity of the original API or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between the authorized agents and the original API or intermediate manufacturer. (In this context "authorized" refers to authorized by the manufacturer.)

17.63 The specific guidance for Certificates of Analysis included in Section 11.4 should be met.

17.7 Handling of Complaints and Recalls

17.70 Agents, brokers, traders, distributors, repackers, or relabellers should maintain records of complaints and recalls, as specified in Section 15, for all complaints and recalls that come to their attention.

17.71 If the situation warrants, the agents, brokers, traders, distributors, repackers, or relabellers should review the complaint with the original API or intermediate manufacturer in order to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.

17.72 Where a complaint is referred to the original API or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, repackers, or relabellers should include any response received from the original API or intermediate manufacturer (including date and information provided).

17.8 Handling of Returns

17.80 Returns should be handled as specified in Section 14.52. The agents, brokers, traders, distributors, repackers, or relabellers should maintain documentation of returned APIs and intermediates.

18 Specific Guidance for APIs Manufactured by Cell Culture/Fermentation

18.1 General

18.10 Section 18 is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone Section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for “classical” processes for production of small molecules and for processes using recombinant and non-recombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.

18.11 The term “biotechnological process” (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this Section. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.

18.12 The term “classical fermentation” refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g. irradiation or chemical mutagenesis) to produce APIs. APIs produced by “classical fermentation” are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.

18.13 Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

18.14 Appropriate controls should be established at all stages of manufacturing to assure intermediate and/or API quality. While this Guide starts at the cell culture/fermentation step, prior steps (e.g. cell banking) should be performed under appropriate process controls. This Guide covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.

18.15 Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for quality of the environment and the frequency of monitoring should depend on the step in production and the production conditions (open, closed, or contained systems).

18.16 In general, process controls should take into account:

- Maintenance of the Working Cell Bank (where appropriate);
- Proper inoculation and expansion of the culture;
- Control of the critical operating parameters during fermentation/cell culture;

- Monitoring of the process for cell growth, viability (for most cell culture processes) and productivity where appropriate;
- Harvest and purification procedures that remove cells, cellular debris and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality;
- Monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production; and
- Viral safety concerns as described in ICH Guideline Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*.

18.17 Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

18.2 Cell Bank Maintenance and Record Keeping

18.20 Access to cell banks should be limited to authorized personnel.

18.21 Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.

18.22 Records of the use of the vials from the cell banks and storage conditions should be maintained.

18.23 Where appropriate, cell banks should be periodically monitored to determine suitability for use.

18.24 See ICH Guideline Q5D *Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products* for a more complete discussion of cell banking.

18.3 Cell Culture/Fermentation

18.30 Where aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.

18.31 Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.

18.32 Personnel should be appropriately gowned and take special precautions handling the cultures.

18.33 Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.

18.34 Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, and sanitized or sterilized.

18.35 Culture media should be sterilized before use when appropriate to protect the quality of the API.

18.36 There should be appropriate procedures in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.

18.37 Records of contamination events should be maintained.

18.38 Shared (multi-product) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

18.4 Harvesting, Isolation and Purification

18.40 Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, should be performed in equipment and areas designed to minimize the risk of contamination.

18.41 Harvest and purification procedures that remove or inactivate the producing organism, cellular debris and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.

18.42 All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

18.43 If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.

18.44 Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

18.5 Viral Removal/Inactivation steps

18.50 See the ICH Guideline Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* for more specific information.

18.51 Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.

18.52 Appropriate precautions should be taken to prevent potential viral contamination from pre-viral to post-viral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.

18.53 The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carry-over (e.g. through equipment or environment) from previous steps.

19 APIs for Use in Clinical Trials

19.1 General

19.10 Not all the controls in the previous sections of this Guide are appropriate for the manufacture of a new API for investigational use during its development. Section 19 provides specific guidance unique to these circumstances.

19.11 The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from pre-clinical stages through clinical stages. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

19.2 Quality

19.20 Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism of approval of each batch.

19.21 A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.

19.22 Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.

19.23 Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.

19.24 Process and quality problems should be evaluated.

19.25 Labelling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

19.3 Equipment and Facilities

19.30 During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use.

19.31 Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

19.4 Control of Raw Materials

19.40 Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.

19.41 In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

19.5 Production

19.50 The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.

19.51 Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

19.6 Validation

19.60 Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, calibration, and, where appropriate, equipment qualification assures API quality during this development phase.

19.61 Process validation should be conducted in accordance with Section 12 when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.

19.7 Changes

19.70 Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.

19.8 Laboratory Controls

19.80 While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.

19.81 A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.

19.82 Expiry and retest dating as defined in Section 11.6 applies to existing APIs used in clinical trials. For new APIs, Section 11.6 does not normally apply in early stages of clinical trials.

19.9 Documentation

19.90 A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

19.91 The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.

19.92 A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.

20 Glossary

Acceptance Criteria

Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) (*or Drug Substance*)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

API Starting Material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

Batch (or Lot)

A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch Number (or Lot Number)

A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

Bioburden

The level and type (e.g. objectionable or not) of micro-organisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Calibration

The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

Computer System

A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions.

Computerized System

A process or operation integrated with a computer system.

Contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

Contract Manufacturer

A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Critical

Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Cross-Contamination

Contamination of a material or product with another material or product.

Deviation

Departure from an approved instruction or established standard.

Drug (Medicinal) Product

The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug Substance

See Active Pharmaceutical Ingredient

Expiry Date (or Expiration Date)

The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Impurity

Any component present in the intermediate or API that is not the desired entity.

Impurity Profile

A description of the identified and unidentified impurities present in an API.

In-Process Control (or Process Control)

Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

Intermediate

A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. (Note: this Guide only addresses those intermediates produced after the point that the company has defined as the point at which the production of the API begins.)

Lot

See Batch

Lot Number see Batch Number

Manufacture

All operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control, release, storage, and distribution of APIs and related controls.

Material

A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs and packaging and labelling materials.

Mother Liquor

The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API and/or impurities. It may be used for further processing.

Packaging Material

Any material intended to protect an intermediate or API during storage and transport.

Procedure

A documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids

Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid, activated carbon, etc).

Process Control

See In-Process Control

Production

All operations involved in the preparation of an API from receipt of materials through processing and packaging of the API.

Qualification

Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA)

The sum total of the organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC)

Checking or testing that specifications are met.

Quality Unit(s)

An organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This 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.

Quarantine

The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

Raw Material

A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reference Standard, Primary

A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be: (1) obtained from an officially recognised source, or (2) prepared by independent synthesis, or (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material.

Reference Standard, Secondary

A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing

Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process, and not reprocessing.

Retest Date

The date when a material should be re-examined to ensure that it is still suitable for use.

Reworking

Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent).

Signature (signed)

See definition for signed

Signed (signature)

The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent

An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification

A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Validation

A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

Validation Protocol

A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected

The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical

The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.