DECISION

No. 5/07.03.2012

on approval of the Guideline on the Good Manufacturing Practice for Medicinal Products for human use

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health No. 1123/18.08.2010, modified through Order of the Minister of Health No. 1601/28.11.2011, reunited on summons of the President of the National Agency for Medicines and Medical Devices in the ordinary meeting of 07.03.2012, in accordance with Article 12(5) of Government Decision No. 734/2010 on establishment, organisation and operation of the National Agency for Medicines and Medical Devices, as amended, adopts the following

DECISION

Art. 1. - The Guideline on the Good Manufacturing Practice for medicinal products for human use is approved, in accordance with the Annex which is integral part of this Decision.

Art. 2. – On the date of this Decision coming into force, Scientific Council Decision No. 23/03.09.2010 on approval of the Guideline on the Good Manufacturing Practice for medicinal products for human use is hereby repealed.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,
Acad. Prof. Dr. Leonida Gherasim

ANNEX

GUIDELINE ON THE GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS FOR HUMAN USE

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 medicinal 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 (EU) whether the products are sold within or outside of the Union.

Order of the Minister of Health No. 905/2006 on approval of the Principles and guidelines for good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use transposes into Romanian legislation Directive No. 2003/94 of the European Commission. Detailed guidelines in accordance with those principles are published in the Guide to Good Manufacturing Practice (GMP) which will be used in assessing applications for manufacturing authorisations and as a basis for inspection of manufacturers of medicinal products for human use.

The principles of GMP and the detailed guidelines are applicable to all operations which require the authorisations referred to in Article 748 of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product (as amended). They are also relevant for pharmaceutical manufacturing processes, such as undertaken in hospital pharmacies.

This Guideline 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 the main GMP requirements for active substances used as starting materials and Part III contains GMP related documents, which clarify regulatory expectations.

Chapters of Part I on "basic requirements" are headed by principles as defined in Order of the Minister of Health No. 905/2006. 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 Article 756 of Law No. 95/2006, Title XVII, 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 Order of the Minister of Health No. 905/2006. The aim of Part III is to clarify regulatory expectations and it is to be viewed as a source of information on current best practices. Details on the applicability will be described separately in each document.

This Guideline 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 Community or national law.

Throughout the Guideline, 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 Manufacturing Authorisation Holder.

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 Guideline, 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 Guideline.

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 National Agency for Medicines and Medical Devices: www.anmdm.ro.

REVISION HISTORY

Date	Revision
October 2001	➢ Amendment of paragraph 42 of Annex 1 ➢ Annex renumbering ➢ Revision of Annex 4 - „manufacture of medicinal gases” ➢ New Annex 13 – “Qualification and validation” ➢ New Annex 14 - “Parametric release” ➢ Revision of Annex 12 - “Manufacture of medicinal products derived from human blood or plasma” ➢ Elimination of Annex 13 - “Homeopathic products” ➢ Amendment of the Glossary
June 2003	➢ Harmonisation and additions in accordance with: - Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use - The introduction of Annex 15 - “Certification by the Qualified Person and batch release” ➢ The introduction to Annex 16 - “Good Manufacturing Practice rules for pharmaceutical active substances‘’
September 2006	➢ Harmonisations and additions in accordance with: - Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended, transposed into Romanian legislation through Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product;

	- Directive 2003/94/EC laying down the principles and guidelines of Good Manufacturing Practice in respect of medicinal products for human use and investigational medicinal products for human use, transposed into Romanian legislation through Order of the Minister of Public Health No. 905/2006. ➢ Reorganisation in accordance with the European Good Manufacturing Practice Guideline: Part I – Basic requirements for medicinal products, Part II – Basic requirements for active substances used as starting materials and Annexes ➢ Introduction of Annex 19 – „Reference and retention samples" ➢ Update of Chapter 1 – "Quality Management" ➢ Update of Annex 1 – "Manufacture of sterile medicinal products" ➢ Update of Annex 12 – "Manufacture of Investigational Medicinal Products" ➢ Renumbering of the Annexes in accordance with the EU GMP Guideline
March 2009	➢ Update of Chapter 1 – "Quality Management" (introduction of the principle of Quality Risk Management) ➢ Update of Part II – "Manufacture of pharmaceutical active substances" (introduction of the principle of Quality Risk Management) ➢ Update of Annex 1 – "Manufacture of sterile medicinal products" ➢ Update of Annex 3 – "Manufacture of radiopharmaceuticals" ➢ Update of Annex 7 – "Manufacture of herbal medicinal products" ➢ Introduction of Annex 20 – "Quality Risk Management"
September 2010	➢ Amendment of Part II – "Manufacture of active pharmaceutical substances" ➢ Amendment of Annex 6 – "Manufacture of medicinal gases" ➢ Amendment of Annex 13 – "Investigational Medicinal Products"

March 2012	➢ Amendment of Chapter 4 – "Documentation" ➢ Amendment of Annex 11 – "Computerised systems" ➢ Amendment of Annex 14 – "Manufacture of medicinal products derived from human blood or plasma" ➢ Introduction of Part III – "GMP-related documents" ➢ Elimination of Annex 20 and its introduction in Part III – "Quality Risk Management"

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PART I

BASIC REQUIREMENTS FOR MEDICINAL PRODUCTS

CHAPTER 1 QUALITY MANAGEMENT

Principle

The Marketing Authorisation Holder must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation 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 all departments and at all levels within the company, by the company's suppliers and by the distributors.

To reliably achieve the quality objective there must be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice, Quality Control and Quality Risk Management. It should be fully documented and its effectiveness monitored. All parts of the Quality Assurance 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 Assurance, Good Manufacturing Practice, Quality Control 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.

Quality assurance

1.1 Quality Assurance is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product; it represents a sum of organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guideline. The system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that:

i. Medicinal products are designed and developed in accordance with the requirements of the Good Manufacturing Practice and the Good Laboratory Practice Guidelines;

ii. Production and control operations are clearly specified and Good Manufacturing Practice adopted;
iii. Managerial responsibilities are clearly specified;
iv. Arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
v. All necessary controls on intermediate products, and any other in-process controls and validations are carried out;
vi. Finished products are correctly processed and checked according to the defined procedures;
vii. 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;
viii. 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;
ix. There is a procedure for Self-Inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Quality Assurance system.

Good Manufacturing Practice for Medicinal Products (GMP)

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

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;
    - appropriate materials, containers and labels;
    - approved procedures and instructions;
    - suitable storage and transport;
iv. instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
v. operators are trained to carry out procedures correctly;
vi. records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated;
vii. records of manufacture including distribution which enable the complete history of a batch to be traced are retained in a comprehensible and accessible form;
viii. the (wholesale) distribution of medicinal products minimises any risk to their quality;
ix. the existence of a withdrawal system of any product batch, from marketing or distribution;
x. complaints about marketed medicinal 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

1.3 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, inspecting and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions in accordance with GMP requirements;
ii. samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by Quality Control;
iii. test methods are validated;
iv. records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out; any deviations are fully recorded and investigated;
v. the finished products contain active ingredients complying with the qualitative and quantitative composition of the Marketing Authorisation, are of the required purity and are enclosed within their proper containers and correctly labelled;
vi. records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification; product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;
vii. no batch of product is released for sale or supply prior to certification by a Qualified Person that it is in accordance with the requirements of the relevant authorisations;
viii. sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

Product quality review

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

(i) A review of starting materials including packaging materials used in the product, especially those from new sources;
(ii) A review of critical in-process controls and finished product results;
(iii) A review of all batches that failed to meet established specification(s) and their investigation;
(iv) A review of all significant deviations or non-compliances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken;
(v) A review of all changes carried out to the processes or analytical methods;
(vi) A review of Marketing Authorisation variations submitted/granted/ refused, including those for third country (export only) dossiers;
(vii) A review of the results of the stability monitoring programme and any adverse trends;

(viii) A review of all quality-related returns, complaints and recalls and the investigations performed at the time;
(ix) A review of adequacy of any other previous product process or equipment corrective actions;
(x) For new marketing authorisations and variations to marketing authorisations, a review of post-marketing commitments;
(xi) The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases etc.
(xii) A review of any contractual/technical arrangements to ensure that they are up to date.

The manufacturer and Marketing Authorisation Holder should evaluate the results of this review, where different, and an assessment made of whether corrective and preventative action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventative actions should be completed in a timely and effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products etc. where scientifically justified.

Where the Marketing Authorisation Holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The Qualified Person responsible for final batch certification together with the Marketing Authorisation Holder should ensure that the quality review is performed in a timely manner and is accurate.

Quality risk management

1.5 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.

1.6 The quality risk management system should ensure that:
- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;
- the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk;

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

CHAPTER II PERSONNEL

Principle

The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of medicinal products relies upon the personnel. 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. The responsibilities placed on any individual should not be so extensive as to present any risk to quality.

2.2 The manufacturer must have an organisational chart. People in responsible positions should have detailed, 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.

Key personnel

2.3 Key Personnel includes 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 760 of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, the Qualified Person(s) designated for the purpose. Normally key positions 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 sections 2.5, 2.6 and 2.7.

2.4 The duties of the Qualified Person(s) are fully described in Article 760 of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, and can be summarised as follows:

a) for medicinal products manufactured within Romania or the European Community, a Qualified Person must ensure that each batch has been produced and tested/checked in accordance with the directives and the marketing authorisation;

b) for medicinal products manufactured outside Romania or the European Community, a Qualified Person must ensure that each imported batch has undergone, in the importing country, the testing specified in Art. 760 (1) b) of Law No. 95/2006;

c) a 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 Art. 760 of Law No. 95/2006.

The persons responsible for these duties must meet the qualification requirements laid down in Article 758 of Law No. 95/2006 and they shall be permanently and continuously at the disposal of the Manufacturing Authorisation Holder to carry out their responsibilities. Their responsibilities may be delegated, but only to other Qualified Person(s).

2.5 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 before they are sent to the Quality Control Department;
iv. to check the 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.

2.6 The head of the Quality Control Department generally has the following responsibilities:

i. to approve or reject, as he sees fit, starting materials, packaging materials, and intermediate, bulk and finished products;
ii. to evaluate batch records;
iii. to ensure that all necessary testing has been carried out;

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

Other duties of the Quality Control Department are summarised in Chapter 6.

2.7 The heads of Production and Quality Control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include:

- the authorisation of written procedures and other documents, including amendments;
- the monitoring and control of the manufacturing environment;
- plant hygiene;
- process validation;
- training;
- the approval and monitoring of suppliers of materials;
- the approval and monitoring of contract manufacturers;
- the designation and monitoring of storage conditions for materials and products;
- the retention of records;
- the monitoring of compliance with the requirements of Good Manufacturing Practice;
- the inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality.

Training

2.8 The manufacturer should provide training for all the personnel whose duties take them into production 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.

2.9 Besides the basic training on the theory and practice of 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.

2.10 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.

2.11 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 also be closely supervised.

2.12 The concept of Quality Assurance and all measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

Personal hygiene

2.13 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 supported by management and widely discussed during training sessions.

2.14 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.

2.15 All steps should be taken to ensure 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.

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

2.17 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.

2.18 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.

2.19 The personnel should be instructed to use hand washing facilities.

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

CHAPTER III 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 Measures 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 handled products, 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.

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.

Quality control areas

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, deionised 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.

CHAPTER 4 DOCUMENTATION

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 must 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 must 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 must be applied with respect to the type of document.

Suitable controls must be implemented to ensure the accuracy, integrity, availability and legibility of documents. Instruction documents must 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):

The Site Master File is a document describing the GMP related activities of the manufacturer.

Instructions (directions, requirements)

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 must be specified where relevant, together with acceptance criteria.

Procedures (otherwise known as Standard Operating Procedures or SOPs) provide 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

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

Certificates of Analysis provide a summary of testing results on samples of products or materials[1] 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 must 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 must 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 must be implemented. Appropriate controls must be in place to ensure the integrity of the record throughout the retention period.

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

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

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

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

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

Good Documentation Practice

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

4.8 Records must 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 must be signed and dated; the alteration must permit the reading of the original information. Where appropriate, the reason for the alteration must be recorded.

Retention of documents

[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.

4.10. It must 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 must 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 must be documented and must take into account the requirements for retention of batch documentation; for example, in the case of process validation data, the accompanying raw data must 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 must describe all documents required to ensure product quality and patient safety.

Specifications

4.13 There must 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 must 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 manufacturer of the material;
   - A sample of printed packaging materials.
b) Directions of 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 must be available for critical steps or if these are purchased or dispatched. The specifications must be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

4.16 Specifications for finished products must 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 formulae and processing instructions

Approved, written Manufacturing Formula and Processing Instructions must exist for each product and batch size to be manufactured. These two documents are often reunited in a single document.

4.17 The manufacturing formula must 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 must 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 must 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, labelling 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 must exist. These must 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 full 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 stations 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 records

4.20 A Batch Processing Record must be kept for each batch processed. It must be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions, and must 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 the manufacturing process;
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) Detailed 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 must be kept for each batch or part batch processed. It must be based on the relevant parts of the Packaging Instructions.

The batch packaging record must 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 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 must be written procedures and records for the receipt of each delivery of each starting material, (including bulk, intermediate or finished products), primary, secondary and printed packaging materials.

4.23 The record of the receipts must 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 must be written procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

Sampling

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

Other documents

4.27 Written release and rejection procedures must 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 must be available to the Qualified Person(s). A system must be in place to indicate special observations and any changes to critical data.

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

4.29 There must 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 of deviations and non-compliances;
- internal quality/GMP compliance audits;
- summaries of records (e.g. product quality review);
- supplier audits.

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

4.31 Logbooks must be kept for major or critical analytical testing, production equipment, and areas where product has been processed. They must 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 must 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 required quality and be in accordance with the relevant manufacturing and marketing authorisations.

General

5.1 Production must 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 must be performed in accordance with written procedures or instructions and, where necessary, recorded.

5.3 All incoming materials must be checked to ensure that the consignment corresponds to the order. Containers must 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 must be investigated, recorded and reported to the Quality Control Department.

5.5 Incoming materials and finished products must 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 must be handled on receipt as though they were starting materials.

5.7 All materials and products must 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, must be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

5.9 Operations on different products must 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 must be protected from microbial and other contamination.

5.11 When working with dry materials and products, special precautions must be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitising materials.

5.12 In all stages of processing, all materials, bulk containers, major items of equipment and, where appropriate, rooms used must 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 must also mention the stage of production.

5.13 Labels applied to containers, equipment or premises must 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 etc.).

5.14 Checks must 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 must be avoided as far as possible. If a deviation occurs, it must be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.

5.16 Access to production premises must be restricted to authorised personnel.

5.17 Normally, the production of non-medicinal products must 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 must be avoided by appropriate technical or organizational measures, such as:

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 must be checked periodically according to set procedures.

Validation

5.21 Validation studies must reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions must be recorded.

5.22 When any new manufacturing formula or method of preparation is adopted, steps must be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, must 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 must be validated.

5.24 Processes and procedures must 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 must involve staff who has a particular and thorough knowledge of the suppliers.

5.26 Starting materials must only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the manufacturer. 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 must 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 must be appropriately labelled (see Chapter 5, section 13). Labels must 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, being tested, 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 must 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 must be identified (see Chapter 6, section 13).

5.31 Only starting materials which have been released by the Quality Control Department and which are within their shelf life must be used in the manufacturing process.

5.32 Starting materials must 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 must be independently checked and the check recorded.

5.34 Materials dispensed for each batch must be kept together and conspicuously labelled as such.

Processing operations: intermediate and bulk products

5.35 Before any processing operation is started, steps must 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 must be kept under appropriate conditions.

5.37 Critical processes must be validated (see "Validation" in this Chapter).

5.38 Any necessary in-process controls and environmental controls must be carried out and recorded.

5.39 Any significant deviation from the expected yield must 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 must be paid to printed materials. They must be stored in adequately secure conditions such as to exclude unauthorised access. Cut labels and other loose printed materials must be stored and transported in separate closed containers so as to avoid mix-ups.
Packaging materials must 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 must be given a specific reference number or identification mark.

5.43 Outdated or obsolete primary packaging material or printed packaging material must be destroyed and this disposal recorded.

Packaging operations

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

5.45 Before packaging operations are begun, steps must 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 must be performed according to an appropriate check-list.

5.46 The name and batch number of the product being handled must be displayed at each packaging station or line.

5.47 All products and packaging materials to be used must be checked on delivery to the packaging department for quantity, identity and compliance with the Packaging Instructions.

5.48 Containers for filling must be clean before filling. Attention must be given to avoiding and removing any contaminants such as glass fragments and metal particles.

5.49 Normally, filling and sealing must be followed as quickly as possible by labelling. If this is not the case, appropriate procedures must be enforced to ensure that no mix-ups or mislabelling can occur.

5.50 The correct performance of any printing operation (such as code numbers, expiry dates) to be done separately or in the course of the packaging must be checked and recorded. Attention must be paid to printing by hand which must be re-checked at regular intervals.

5.51 Special care must 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 must 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 must be distinct and resistant to fading or erasing.

5.54 On-line control of the product during packaging must include at least checking the following:

a) general appearance of the packages;
b) whereas 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 must not be returned.

5.55 Products which have been involved in an unusual event must only be reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed records of this operation must be kept.

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 must be investigated and satisfactorily accounted for before batch release.

5.57 Upon completion of a packaging operation, any unused batch-coded packaging materials must be destroyed and the destruction recorded. A documented procedure must be followed if printed materials not containing a batch number are returned to stock.

Finished products

5.58 Finished products must be held in quarantine until final batch 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 is described in Chapter 6 (Quality Control).

5.60 After release, finished products must be stored as usable stock under conditions established by the manufacturer.

Rejected, recovered and returned materials

5.61 Rejected materials and products must be clearly marked as such and stored separately in restricted areas. They must either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken must be approved and recorded by authorised personnel.

5.62 The reprocessing of rejected products must 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 of the reprocessing must be kept.

5.63 The partial or total recovery of earlier batches which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture must be authorised beforehand. This recovery must be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery must 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, must be considered by the Quality Control Department.

5.65 Products returned from the market and which are no longer under the control of the manufacturer must 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 must all be taken into account in this assessment. Where any doubt arises over the quality of the product, it must not be considered suitable for re-issue or re-use, although basic chemical reprocessing to recover active ingredient may be possible. Any action taken must be appropriately recorded.

CHAPTER VI QUALITY CONTROL

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).

6.1 Each Marketing Authorisation Holder must have a Quality Control Department. This department must 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 must be carried out in accordance with written procedures and, where necessary, recorded.

6.3 Finished product assessment must embrace all relevant factors, including manufacturing conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification and examination of the finished pack.

6.4 Quality Control personnel must have access to production areas for sampling and investigation as appropriate.

Good Quality Control Laboratory Practice

6.5 Control laboratory premises and equipment must meet the general and specific requirements for Quality Control areas given in Chapter 3.

6.6 The personnel, premises, and equipment in the laboratories must be appropriate to the tasks imposed by the nature and scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed in Chapter 7, Contract Manufacture and Analysis, can be accepted for particular reasons, but this must be stated in the Quality Control records.

Documentation

6.7 Laboratory documentation must follow the principles given in Chapter 4. An important part of this documentation deals with Quality Control and the following details must 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 must be retained for one year after the expiry date of the batch and at least 5 years after the certification referred to in Article 760 (3) of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product.

6.9 For some types 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 must be retained and readily available.

Sampling

6.11 The sample taking must 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 subdivision of the sample, where appropriate;
- 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 hazardous materials;
- the storage conditions;
- instructions for the cleaning and storage of sampling equipment.

6.12 Reference samples must 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 manufacturing process).

6.13 Sample containers must 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 Reference samples in each finished product batch must be kept one year after the expiry date. Finished products must usually be kept in their final packaging and in accordance with the required conditions. Starting material samples (except for solvents, gases and water) must be kept at least two years after the product's release, if their stability allows it. This period may be shortened if the respective product's specification denotes the fact that these are less stable. A sufficient amount of reference samples must be kept, to allow at least one complete retesting.

Testing

6.15 Analytical methods must be validated. All testing operations described in the marketing authorisation must be carried out according to the approved methods.

6.16 The results obtained must be recorded and checked to make sure that they are consistent with each other. Any calculations must be critically examined.

6.17 The tests performed must be recorded and the records must 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, must be performed according to methods approved by Quality Control and the results recorded.

6.19 Particular attention must be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards and culture media. They must be prepared in accordance with written procedures.

6.20 Laboratory reagents intended for prolonged use must be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and culture media must be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardization and the last current factor must be indicated.

6.21 Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents and reference standards) must be indicated on the container. Instructions for use and storage must 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, must, where appropriate, be quarantined before use. They must be maintained and controlled in a manner that ensures their suitability for the intended use. They must be identified, and adequate records must be maintained, showing the history of their use.

CHAPTER 7 CONTRACT MANUFACTURE AND ANALYSIS

Principle

Contract manufacture and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product or work 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 contract must clearly state the way in which the Qualified Person releasing each batch of product for sale 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 authorisations. 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 must be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.

7.2 All arrangements for contract manufacture and analysis including any proposed changes in technical or other arrangements must be in accordance with the marketing authorization for the concerned product.

Contract giver

7.3 The contract giver is responsible for assessing the competence of the contract acceptor to carry out successfully the work required and for ensuring by means of the contract that the principles and guidelines of GMP as interpreted in this Guideline are followed.

7.4 The contract giver must provide the contract acceptor with all the information needed to carry out the contracted operations correctly in accordance with the marketing authorisation and any other legal requirements. The Contract Giver must 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.

7.5 The contract giver must ensure that all processed products and materials delivered to him by the contract acceptor comply with their specifications or that the products have been released by a Qualified Person.

Contract acceptor

7.6 The contract acceptor must have adequate premises and equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the contract giver. Contract manufacture may be undertaken only by a manufacturer who is the Marketing Authorisation Holder.

7.7 The contract acceptor must ensure that all products or materials delivered to him are suitable for their intended purpose.

7.8 The Contract Acceptor must 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. Arrangements made between the Contract Acceptor and any third party must ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract acceptor.

7.9 The contract acceptor must refrain from any activity which may adversely affect the quality of the product manufactured and/or analysed for the contract giver.

The contract

7.10 A contract must be drawn up between the contract giver and the contract acceptor which specifies their respective responsibilities relating to the manufacture and control of the product. Technical issues of the contract must be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and Good Manufacturing Practice. All arrangements for manufacture and analysis must be in accordance with the marketing authorisation and agreed by both parties.

7.11 The contract must specify the way in which the Qualified Person releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of the Marketing Authorisation.

7.12 The contract must describe clearly who is responsible for purchasing materials, testing and releasing materials, undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract must state whether or not the Contract Acceptor must take samples at the premises of the manufacturer.

7.13 Manufacturing, analytical and distribution records, as well as reference samples, must 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 must be accessible and specified in the defect/recall procedures of the contract giver.

7.14 The contract must permit the Contract Giver to visit the facilities of the contract acceptor.

7.15 In the case of contract analysis, the contract acceptor must understand that he is subject to inspection by competent authorities.

CHAPTER 8 COMPLAINTS AND PRODUCT RECALL

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 829 of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, a system must be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

Complaints

8.1 A person must 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 must be made aware of any complaint, investigation or recall.

8.2 There must 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 must be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control must normally be involved in the study of such problems.

8.4 If a product defect is discovered or suspected in a batch, consideration must 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 must be investigated.

8.5 All decisions and measures taken as a result of a complaint must be recorded and referenced to the corresponding batch records.

8.6 Complaints records must be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed medicinal products.

8.7 The National Agency for Medicines and Medical Devices must 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

8.8 A person must be designated as responsible for execution and co-ordination of recalls and must be supported by sufficient staff to handle all the aspects of the recalls with the

appropriate degree of urgency. This responsible person must normally be independent of the sales and marketing organisation. If this person is not the Qualified Person, the latter must be made aware of any recall operation.

8.9 Written procedures must be established in view of organising recall activities; these must be periodically checked and updated, when required.

8.10 Recall operations must be capable of being initiated promptly and at any time.

8.11 All Competent Authorities of all countries to which products may have been distributed must be informed promptly if products are intended to be recalled because they are, or are suspected of being defective.

8.12 Distribution records must be readily available to the person(s) responsible for recalls, and must contain sufficient information on wholesalers and directly supplied customers (with addresses, phone number, inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples.

8.13 Recalled products must be identified and stored separately in a secure area while awaiting a decision on their fate.

8.14 The progress of the recall process must be recorded and a final report issued, including reconciliation between the delivered and recovered quantities of the products.

8.15 The effectiveness of the arrangements for recalls must be evaluated regularly.

CHAPTER 9 SELF-INSPECTION

Principle

Self inspections must 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, must 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 must 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 must be recorded. Reports must contain all the observations made during inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken must also be recorded.

BASIC REQUIREMENTS FOR ACTIVE SUBSTANCES USED AS STARTIN MATERIALS

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1. INTRODUCTION

1.1 Objective

This Guideline is 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 this Guideline, "manufacturing" includes all operations of receipt of materials, production, packaging, repackaging, labelling, relabeling, 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 Guideline, or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance.

The GMP Guideline as a whole does neither 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.

This Guideline is not intended to define registration requirements or modify pharmacopoeial requirements and does 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

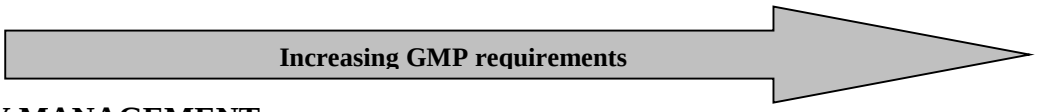
This Guideline applies to the manufacture of active substances for medicinal products for both human and veterinary use. They apply to the manufacture of sterile active substances only up to the point immediately prior to the active substance being rendered sterile. The sterilisation and aseptic processing of sterile active substances are not covered, but should be performed in accordance with the principles and guidelines of GMP as laid down in the Order of the Minister of Public Health No. 905/2006 and interpreted in the GMP Guideline including its Annex 1.
This Guideline excludes whole blood and plasma, however it includes the active substances that are produced using blood or plasma as raw materials. Finally, this Guideline does not apply to bulk-packaged medicinal products. It applies to all other active starting materials subject to any derogations described in the Annexes to the GMP Guideline, particularly to Annexes 2 to 7 where supplementary guidance for certain types of active substance may be found.

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 this Guideline.
This Guideline does 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 Guideline and these therefore should only be applied in the context of Part I.

TABLE 1: Application of this Guideline to API manufacturing

Type of manufacturing	**Application of this Guideline 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
Herbal extracts used as API	Collection of plants	Cutting, mixing and/or initial processing	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(s)		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 the master cell bank and the working cell bank	Maintenance of the cell bank	cell culture and/or fermentation	Isolation and purification	Physical processing and packaging
„Classical" fermentation to produce an API	Establishment of the 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 staff.

2.12. The management quality system 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 fulfils 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 intermediate medicinal products 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;
11. Making sure that effective systems are used for maintaining and calibrating critical equipment;
12. Making sure that materials are appropriately tested and the results are reported;
13. Making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates (where appropriate); and
14. Performing product quality reviews (as defined in Section 2.5).

2.4. Responsibility for production activities

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

l. 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 preapproved 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, where appropriate, modified facilities and equipment are qualified.

2.5. Internal audits (Self-inspections)

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. Established 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-compliances 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 actions or any revalidation should be undertaken. Reasons for such corrective actions 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 intermediate medicinal products 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 hygiene.

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 required.

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 prior to the 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;
- Manufacturing 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-siphon age, 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 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 activity (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 separated 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 appropriately designed and of 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:

- 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 ensuring 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 intermediates or APIs manufactured using this equipment since the last successful calibration.

5.4. Computerised systems

5.40. GMP related computerized systems should be validated. The depth and scope of validation depend 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 unauthorised 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 authorised, 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 computerised 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, replacement 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 API's; 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 compliance with established specifications; and

- The final decision regarding rejected raw materials, intermediates or API labelling 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 sequence to be followed;

  - the 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 modification 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. MATERIAL 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 according to 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 impurity traces;
- 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 comply with the 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 fibre 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 effect 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 of 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 unauthorised 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 forma 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 compliance with the 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. Storage procedures

10.10. Facilities should be available for the storage of all materials under adequate 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 authorised 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 API/intermediate transportation 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 CONTROL

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 organisational 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 fibre 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 APIs in terms of its critical product characteristics;
- 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

12.3. 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 section 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 reviews 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/sanitisation 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 enforcing 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 REUSE 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 the 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. Prior to taking the decision to rework batches that do not conform to established standards or specifications, an investigation into the reason for non-compliance 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 the complainant;
- Name (and, where appropriate, title) and phone number of person submitting the complaint;
- Nature of complaint (including name and batch number of the API);
- Date of receipt of the complaint;
- 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 (LABORATORIES INCLUDED)

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 relabelers 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 the original manufacturer;
- Address of the original manufacturer;
- Purchases orders;
- Transportation documentation;
- Receipt documents;
- Name 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, relabeling and storage of APIs and intermediates

17.40. Repackaging, relabeling 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. Information transfer

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 relabeler 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 authorised agents, depending on the legal relationship between the authorised agents and the original API or intermediate manufacturer. (In this context "authorised" refers to authorised 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 refers 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 RULES 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 Guideline 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 the:

- 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 authorised 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 layers, 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 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 organisational units.

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

19.24. Process and quality issues 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 to be used in clinical trials is usually 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 for marketing authorisation.

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 (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 (Lot number)

A unique combination of numbers, letters and/or symbols identifying a batch o (or lot) and based on 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.

Computerised 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.

Expected yield

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.

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/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 that the company has defined as the point at which the production of the API begins.)

Lot

See Batch.

Lot number

See Batch number.

Material

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

Medicinal product

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

Medicinal substance

See Active pharmaceutical ingredient.

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.

Primary reference standard

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.

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 participate themselves in a chemical or biological reaction (e.g. filter aid, activated carbon, etc).

Process control

See In-process controls

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/control unit

An organisational unit independent of production which fulfils 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.

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).

Secondary reference standard

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.

Signature

The record of the individual who performed a certain action/review. This record may contain initials, a 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. “Compliance with specification” means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Theoretical yield

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.

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.

PART II

BASIC REQUIREMENTS FOR MEDICINAL PRODUCTS

GUIDELINE ON THE PREPARATION OF A SITE MASTER FILE

I. INTRODUCTION

1.1. The Site Master File is prepared by the pharmaceutical manufacturer and should contain specific information about the quality management policies and activities of the site, the production and/or quality control of pharmaceutical manufacturing operations carried out at the named site and any closely integrated operations at adjacent and nearby buildings. If only part of a pharmaceutical operation is carried out on the site, a Site Master File need only describe those operations, e.g. analysis, packaging, etc.

1.2. When submitted to the National Agency for Medicines and Medical Devices, the Site Master File should provide clear information on the manufacturer's Good Manufacturing Practice (GMP) related activities that can be useful in general supervision and in the efficient planning and undertaking of GMP inspections.

1.3. A Site Master File should contain adequate information but, as far as possible, not exceed 25-30 pages plus annexes. Simple plans, outline drawings or schematic layouts are preferred instead of narratives. The Site Master File, including annexes, should be readable when printed on A4 paper sheets.

1.4. The Site Master File should be a part of documentation belonging to the quality management system of the manufacturer and kept updated accordingly. The Site Master File should have an edition number, the date it becomes effective and the date by which it has to be reviewed. It should be subject to regular review to ensure that it is up to date and representative of current activities. Each Annex can have an individual effective date, allowing for independent updating.

II. PURPOSE

The aim of this Guideline is to guide the manufacturer of medicinal products in the preparation of a Site Master File that is useful to the National Agency for Medicines and Medical Devices in planning and conducting GMP inspections.

III. CONTENT OF SITE MASTER FILE

1. GENERAL INFORMATION ON THE MANUFACTURER

1.1. Contact information on the manufacturer

- Name and official address of the manufacturer;
- Names and street addresses of the site, buildings and production units located on the site;

- Contact information of the manufacturer including 24 hrs telephone number of the contact personnel in the case of product defects or recalls.
- Identification number of the site as e.g. GPS details, or any other geographic location system, D-U-N-S (Data Universal Numbering System) Number (a unique identification number provided by Dun & Bradstreet) of the site[2]

1.2. Pharmaceutical manufacturing activities, as authorised by the National Agency for Medicines and Medical Devices or by the competent authority in a third country

- Copy of the valid manufacturing authorisation issued by the relevant Competent Authority in Annex 1; or when applicable, reference to the EudraGMP database. If the Competent Authority does not issue manufacturing authorizations, this should be stated.
- Brief description of manufacture, import, export, distribution and other activities as authorized by the relevant Competent Authorities (including foreign authorities from third countries) with authorized dosage forms/activities;
- Type of products currently manufactured on-site (list in Annex 2) where not covered by Annex 1 or EudraGMP entry;
- List of GMP inspections of the site within the last 5 years, including the names/country of the Competent Authority having performed the inspection. A copy of current GMP certificate (Annex 3) or reference to the EudraGMP database should be included, if available.

1.3. Any other manufacturing activity carried out on the site

- Description of non-pharmaceutical activities on-site, if any.

2. QUALITY MANAGEMENT SYSTEM OF THE MANUFACTURER

2.1. The quality management system of the manufacturer

- Brief description of the quality management systems run by the company and reference to the standards used;
- Responsibilities related to the maintaining of quality system including senior management;
- Information of activities for which the site is accredited and certified, including dates and contents of accreditations, names of accrediting bodies.

2.2. Release procedure of finished products

- Detailed description of qualification requirements (education and work experience) of the Authorised Person(s)/Qualified Person(s) responsible for batch certification and releasing procedures;
- General description of batch certification and releasing procedure;
- Role of Authorised Person/Qualified Person in quarantine and release of finished products and in assessment of compliance with the Marketing Authorisation;
- The arrangements between Authorised Persons/Qualified Persons when several Authorised Persons/Qualified Persons are involved;
- Statement on whether the control strategy employs Process Analytical Technology (PAT) and/or Real Time Release or Parametric Release.

2.3. Management of suppliers and contractors

- A brief summary of the establishment/knowledge of supply chain and the external audit program;
- Brief description of the qualification system of contractors, manufacturers of active pharmaceutical ingredients (API) and other critical materials suppliers;

[2] A-D-U-N-S reference is required for Site Master Files submitted to EU/EEA authorities for manufacturing sites located outside of the EU/EEA.

- Measures taken to ensure that products manufactured are compliant with TSE (Transmitting animal spongiform encephalopathy) guidelines.
- Measures adopted where counterfeit/falsified products, bulk products (i.e. unpacked tablets), active pharmaceutical ingredients or excipients are suspected or identified.
- Use of outside scientific, analytical or other technical assistance in relation to manufacture or analysis;
- List of contract manufacturers and laboratories including the addresses and contact information and flow charts of supply-chains for outsourced manufacturing and Quality Control activities; e.g. sterilization of primary packaging material for aseptic processes, testing of starting raw-materials etc., should be presented in Annex 4;
- Brief overview of the responsibility sharing between the contract giver and acceptor with respect to compliance with the Marketing Authorization (where not included under 2.2).

2.4. Quality Risk Management (QRM)

- Brief description of QRM methodologies used by the manufacturer;
- Scope and focus of QRM including brief description of any activities which are performed at corporate level, and those which are performed locally; any application of the QRM system to assess continuity of supply should be mentioned;

2.5. Product Quality Reviews

- Brief description of methodologies used

3. PERSONNEL

- Organisation chart showing the arrangements for quality management, production and quality control positions/titles in Annex 5, including senior management and Qualified Person(s);
- Number of employees engaged in the quality management, production, quality control, storage and distribution respectively;

4. PREMISES AND EQUIPMENT

4.1. PREMISES

- Brief description of the plant; size of the site and list of buildings. If the production for different markets, i.e. for local, EU, USA etc. takes place in different buildings on the site, the buildings should be listed with destined markets identified (if not identified under 1.1);
- Simple plan or description of manufacturing areas with indication of scale (professional drawings are not required);
- Layout of the production areas (in Annex 6) showing the room classification and pressure differentials between adjoining areas and indicating the production activities (i.e. compounding, filling, packaging, etc.) in the rooms;
- Layouts of warehouses and storage areas, with special areas for the storage and handling of highly toxic, hazardous and sensitising materials indicated, if applicable;
- Brief description of specific storage conditions if applicable, but not indicated in the layouts.

4.1.1. Brief description of heating, ventilation and air conditioning (HVAC) systems

- Principles for defining the air supply, temperature, humidity, pressure differentials and air change rates, policy of air recirculation (%);

4.1.2 Brief description of water systems

- Quality reference of water produced;
- Schematic drawings of the Systems in Annex 7

4.1.3. Brief description of other relevant utilities, such as steam, compressed air, nitrogen, etc.

4.2. Equipment

4.2.1. Listing of major production and control laboratory equipment with critical pieces of equipment identified should be provided in Annex 8.

4.2.2. Cleaning and sanitation

- Brief description of cleaning and sanitation methods of product contact surfaces (i.e. manual cleaning, automatic Clean-in-Place, etc.).

4.2.3. GMP critical computerised systems

- Description of GMP critical computerised systems (excluding equipment specific Programmable Logic Controllers (PLCs)

5. DOCUMENTATION

- Description of documentation system (i.e. electronic, manual);
- When documents and records are stored or archived off-site (including pharmacovigilance data, when applicable): List of types of documents/records, name and address of storage site and an estimate of time required retrieving documents from the off-site archive.

6. PRODUCTION

6.1. Type of products (References to Annex 1 or 2 can be made):

- Type of products manufactured including:
  - List of dosage forms of both human and veterinary products which are manufactured on the site;
  - List of dosage forms of investigational medicinal products (IMP) manufactured for any clinical trials on the site, and when different from the commercial manufacturing, information of production areas and personnel.
- Toxic or hazardous substances handled (e.g. with high pharmacological activity and/or with sensitising properties);
- Product types manufactured in a dedicated facility or on a campaign basis, if applicable;
- Process Analytical Technology (PAT) applications, if applicable: general statement of the relevant technology, and associated computerized systems.

6.2. Process validation

- Brief description of general policy for process validation;
- Politics on reprocessing or reworking.

6.3. Material management and warehousing

- Arrangements for the handling of starting materials, packaging materials, bulk and finished products including sampling, quarantine, release and storage;
- Arrangements for the handling of rejected materials and products.

7. QUALITY CONTROL

- Description of the Quality Control activities carried out on the site in terms of physical, chemical, microbiological and biological testing.

8. DISTRIBUTION, COMPLAINTS, PRODUCT DEFECTS AND RECALLS

8.1.Distribution (to the part under the responsibility of the manufacturer)

- Types (wholesale licence holders, manufacturing licence holders, etc.) and locations (EU/EEA, USA, etc.) of the companies to which the products are shipped from the site;
- Description of the system used to verify that each customer / recipient is legally entitled to receive medicinal products from the manufacturer;
- Brief description of the system to ensure appropriate environmental conditions during transit, e.g. temperature monitoring/ control;

- Arrangements for product distribution and methods by which product traceability is maintained;
- Measures taken to prevent manufacturers' products to fall in the illegal supply chain.

8.2.Complaints, product defects and recalls

- Brief description of the system for handling complaints, product defects and recalls.

9. SELF INSPECTIONS

- Short description of the self-inspection system with focus on criteria used for selection of the areas to be covered during planned inspections, practical arrangements and follow-up activities.

Annex 1	Copy of valid manufacturing authorisation
Annex 2	List of dosage forms manufactured including the INN-names or common name (as available) of active pharmaceutical ingredients (API) used
Annex 3	Copy of valid GMP certificates
Annex 4	List of contract manufacturers and laboratories including the addresses and contact information, and flow-charts of the supply chains for these outsourced activities
Annex 5	Organisational charts
Annex 6	Lay outs of production areas including material and personnel flows, general flow charts of manufacturing processes of each product type (dosage form)
Annex 7	Schematic drawings of water systems
Annex 8	List of major production and laboratory equipment

QUALITY RISK MANAGEMENT

1. Introduction

Quality Risk Management may apply not only to the manufacturing environment but also in relation to pharmaceutical development and to the issue of the quality-related section of the marketing authorisation dossier. Moreover, this Guideline also applies to the regulatory authorities in the field of the assessment of the quality-related section of the marketing authorisation dossier, GMP inspections and the dealing with suspected quality non-compliances.

However, for the sake of coherence, the text has been included in 2010 in the GMP Guideline as Annex 20. Ever since Part III to the Guideline on the Good Manufacturing Practice has been created, it has been concluded that Part II is more convenient for its publication.

As part of the enforcement within the EU of the ICH Q9 Guideline, an amendment to Chapter 1 of the GMP Guideline has been introduced in 2010. This amendment has incorporated Quality Risk Management principles into this chapter.

The body of this document, namely the former Annex 20, maintains its optional status and provides examples of processes and applications related to the Quality Risk Management.

Introduction

Risk management principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries.

Although there are some examples of the use of *quality risk management* in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. In addition, the importance of quality systems has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system.

It is commonly understood that *risk* is defined as the combination of the probability of occurrence of *harm* and the *severity* of that harm. However, achieving a shared understanding of the application of risk management among diverse *stakeholders* is difficult because each

stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm.

In relation to medicinal products, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance.

The manufacturing and use of a medicinal product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product quality should be maintained throughout the *product lifecycle* such that the attributes that are important to the *quality* of the drug (medicinal) product remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, the use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks and can beneficially affect the extent and level of direct regulatory oversight.

The purpose of this document is to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, yet supports other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk based decisions, both by regulators and industry, regarding the quality of drug substances and drug (medicinal) products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements.

It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures e.g. standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable. Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators.

2. Scope

This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labelling materials in drug (medicinal) products, biological and biotechnological products).

3. Principles of quality risk management

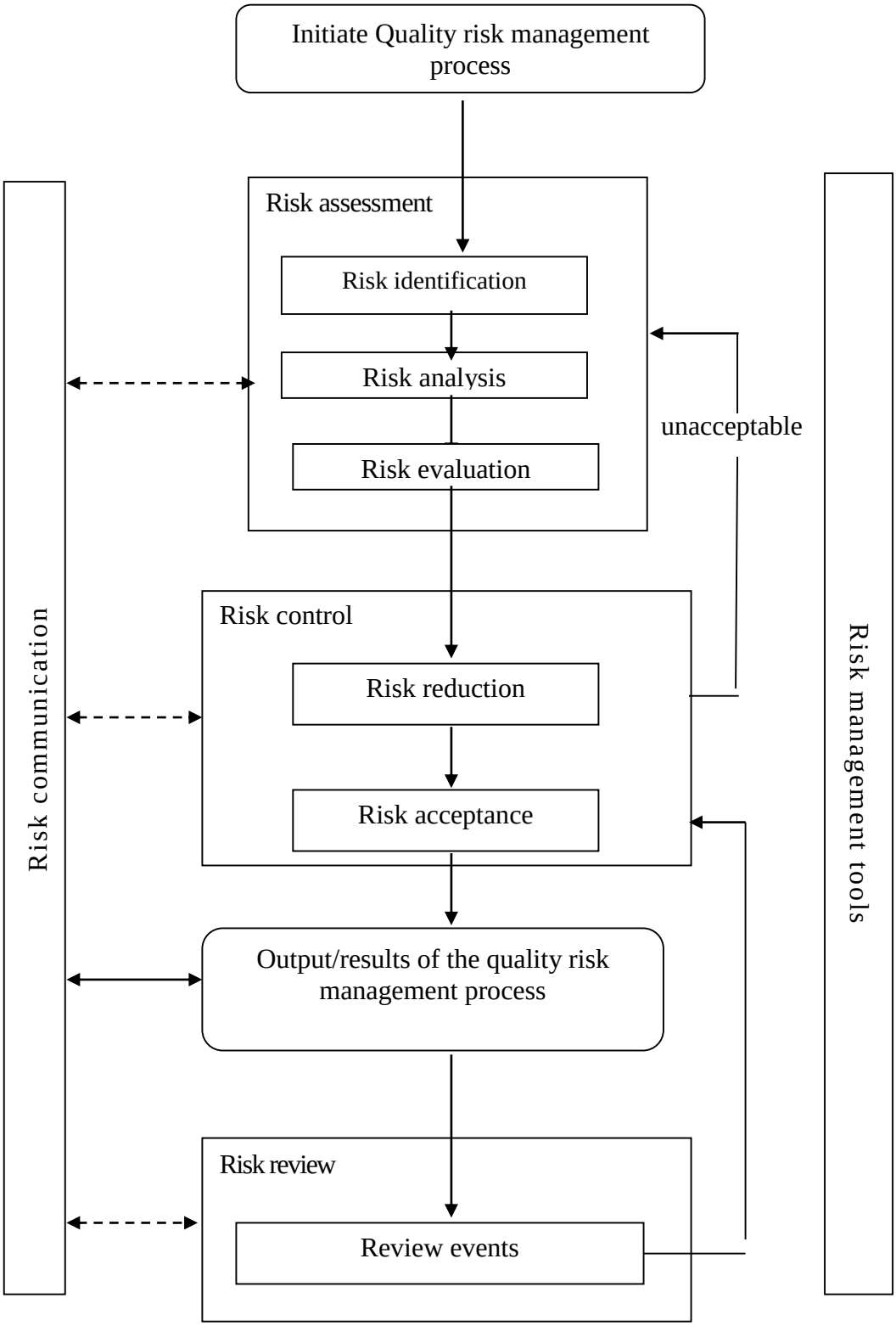
Two primary principles of quality risk management are:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.

4. General quality risk management process

Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product across the product lifecycle. A model for quality risk management is outlined in the diagram (Figure 1); other models could be used. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Figure 1: Overview of a typical Quality risk management process



Decision nodes are not shown in the diagram above because decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models or even to terminate the risk management process based upon information that supports such a decision.

Note: "unacceptable" in the flowchart does not only refer to statutory, legislative or regulatory requirements, but also to the need to revisit the risk assessment process.

4.1. Responsibilities

Quality risk management activities are usually, but not always, undertaken by interdisciplinary teams. When teams are formed, they should include experts from the appropriate areas (e.g. quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics and clinical) in addition to individuals who are knowledgeable about the quality risk management process.

Decision makers should:

- take responsibility for coordinating quality risk management across various functions and departments of their organization; and
- make sure that a quality risk management process is defined, deployed and reviewed and that adequate resources are available.

4.2. Initiating a quality risk management process

Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following:

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk;
- Assemble background information and/ or data on the potential hazard, harm or human health impact relevant to the risk assessment;
- Identify a leader and necessary resources;
- Specify a timeline, deliverables and appropriate level of decision making for the risk management process.

4.3. Risk assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below).

Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool (see examples in section 5) and the types of information needed to address the risk question will be more readily identifiable. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses the "What might go wrong?" question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

Risk evaluation compares the identified and analysed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help identify its limitations. Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), and probability of detection of problems.

The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as “high”, “medium”, or “low”, which should be defined in as much detail as possible. Sometimes a "risk score" is used to further define descriptors in risk ranking. In quantitative risk assessments, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a time. Alternatively, some risk management tools use a relative risk measure to combine multiple levels of severity and probability into an overall estimate of relative risk. The intermediate steps within a scoring process can sometimes employ quantitative risk estimation.

4.4. Risk control

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.

Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level (see Fig. 1). Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified. For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

4.5. Risk communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process (see Fig. 1: dashed arrows). The output/result of the quality risk management process should be appropriately communicated and documented (see Fig. 1: solid arrows). Communications might include those among interested parties; e.g., regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc. The included information might relate to the experience, nature, form, probability, severity, acceptability,

control, treatment, detectability or other aspects of risks to quality. Communication need not be carried out for each and every risk acceptance. Between the industry and regulatory authorities, communication concerning quality risk management decisions might be effected through existing channels as specified in regulations and guidances.

4.6. Risk review

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented. The output/results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g. results of product review, inspections, audits, change control) or unplanned (e.g. root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions (section 4.4).

5. Risk management methodology

Quality risk management supports a scientific and practical approach to decision-making. It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk.

Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/or internal procedures) based on, for example, compilation of observations, trends and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations and allocation of resources.

Additionally, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/or internal procedures (e.g., standard operating procedures). Below is a non-exhaustive list of some of these tools (further details in Annex 1 and chapter 8):

- Basic risk management facilitation methods (flowcharts, check sheets etc.);
- Failure Mode Effects Analysis (FMEA);
- Failure Mode, Effects and Criticality Analysis (FMECA);
- Fault Tree Analysis (FTA);
- Hazard Analysis and Critical Control Points (HACCP);
- Hazard Operability Analysis (HAZOP);
- Preliminary Hazard Analysis (PHA);
- Risk ranking and filtering;
- Supporting statistical tools.

It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug (medicinal) product quality. Quality risk management methods and the supporting statistical tools can be used in combination (e.g. Probabilistic Risk Assessment). Combined use provides flexibility that can facilitate the application of quality risk management principles.

The degree of rigor and formality of quality risk management should reflect available knowledge and be commensurate with the complexity and/or criticality of the issue to be addressed.

6. Integration of quality risk management into industry and regulatory operations

Operations

Quality risk management is a process that supports science-based and practical decisions when integrated into quality systems (see Annex II). As outlined in the introduction, appropriate use of quality risk management does not obviate industry's obligation to comply with regulatory requirements. However, effective quality risk management can facilitate better and more informed

decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight. In addition, quality risk management can facilitate better use of resources by all parties.

Training of both industry and regulatory personnel in quality risk management processes provides for greater understanding of decision-making processes and builds confidence in quality risk management outcomes.

Quality risk management should be integrated into existing operations and documented appropriately. Annex II provides examples of situations in which the use of the quality risk management process might provide information that could then be used in a variety of pharmaceutical operations. These examples are provided for illustrative purposes only and should not be considered a definitive or exhaustive list. These examples are not intended to create any new expectations beyond the requirements laid out in the current regulations.

Examples for regulatory operations (see Annex II):

- Quality management

Examples for industry operations and activities (see Annex II):

- Development
- Facility, equipment and utilities
- Materials management
- Production
- Laboratory control and stability testing
- Packaging and labelling

Examples for regulatory operations (see Annex II)

- Inspection and assessment activities

While regulatory decisions will continue to be taken on a regional basis, a common understanding and application of quality risk management principles could facilitate mutual confidence and promote more consistent decisions among regulators on the basis of the same information. This collaboration could be important in the development of policies and guidelines that integrate and support quality risk management practices.

7. Definitions

Decision maker(s) – Person(s) with the competence and authority to make appropriate and timely quality risk management decisions

Detectability - the ability to discover or determine the existence, presence, or fact of a hazard

Harm – damage to health, including the damage that can occur from loss of product quality or availability

Hazard - the potential source of harm (ISO/IEC Guide 51)

Product Lifecycle – all phases in the life of the product from the initial development through marketing until the product's discontinuation

Quality – the degree to which a set of inherent properties of a product, system or process fulfils requirements (see ICH Q6a definition specifically for "quality" of drug substance and drug (medicinal) products.)

Quality risk management – a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle

Quality system – the sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.

Requirements – the explicit or implicit needs or expectations of the patients or their surrogates (e.g. health care professionals, regulators and legislators). In this document, "requirements" refers not only to statutory, legislative, or regulatory requirements, but also to such needs and expectations.

Risk – the combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51)

Risk acceptance – the decision to accept risk (ISO Guide 73)

Risk analysis – the estimation of the risk associated with the identified hazards
Risk assessment – a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.
Risk communication – the sharing of information about risk and risk management between the decision maker and other stakeholders
Risk control – actions implementing risk management decisions (ISO Guide 73)
Risk evaluation – the comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk
Risk identification – the systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description
Risk management – the systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk
Risk reduction – actions taken to lessen the probability of occurrence of harm and the severity of that harm
Risk review – review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk
Severity – a measure of the possible consequences of a hazard
Stakeholder – any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authorities and industry
Trend – a statistical term referring to the direction or rate of change of a variable(s)

8. References

ICH Q8 Pharmaceutical development
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Annex I: Risk management methods and tools

The purpose of this Annex is to provide a general overview of and references for some of the primary tools that might be used in quality risk management by industry and regulators. The references are included as an aid to gain more knowledge and detail about the particular tool. This

is not an exhaustive list. It is important to note that no tool or set of tools is applicable to every situation in which a quality risk management procedure is used.

I.1 Basic risk management facilitation methods

Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision-making are:

- flowcharts
- check sheets
- process mapping
- cause and effect diagrams (also called an Ishikawa or fish bone diagram)

I.2 Failure mode effects analysis (FMEA)

FMEA (see IEC 60812) provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.

Potential areas of use

FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities.

FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/ results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.

I.3 Failure mode, effects and criticality analysis (FMECA)

FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode Effect and Criticality Analysis (FMECA; see IEC 60812). In order for such an analysis to be performed, the product or process specifications should be established. FMECA can identify places where additional preventive actions might be appropriate to minimize risks.

Potential area(s) of use

FMECA application in the pharmaceutical industry should mostly be utilized for failures and risks associated with manufacturing processes; however, it is not limited to this application. The output of an FMECA is a relative risk "score" for each failure mode, which is used to rank the modes on a relative risk basis.

1.4 Fault tree analysis (FTA)

The FTA tool (see IEC 61025) is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or sub-system) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). FTA relies on the experts' process understanding to identify causal factors.

Potential area(s) of use

FTA can be used to establish the pathway to the root cause of the failure. FTA can be used to investigate complaints or deviations in order to fully understand their root cause and to ensure that intended improvements will fully resolve the issue and not lead to other issues (i.e. solve one problem yet cause a different problem). Fault Tree Analysis is an effective tool for evaluating how multiple factors affect a given issue. The output of an FTA includes a visual representation of failure modes. It is useful both for risk assessment and in developing monitoring programs.

I.5. Hazard Analysis and Critical Control Points (HACCP)

HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety (see WHO Technical Report Series No 908, 2003 Annex 7). It is a structured approach that applies technical and scientific principles to analyse, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of medicinal products.

HACCP consists of the following seven steps:

(1) conduct a hazard analysis and identify preventive measures for each step of the process;
(2) determine the critical control points;
(3) establish critical limits;
(4) establish a system to monitor the critical control points;
(5) establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control;
(6) establish system to verify that the HACCP system is working effectively;
(7) establish a record-keeping system.

Potential area(s) of use

HACCP might be used to identify and manage risks associated with physical, chemical and biological hazards (including microbiological contamination). HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of critical control points. The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other life cycle phases.

I.6 Hazard operability analysis (HAZOP)

HAZOP (see IEC 61882) is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called "guide-words". "Guide-words" (e.g., No, More, Other Than, Part of, etc.) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions. It often uses a team of people with expertise covering the design of the process or product and its application.

Potential area(s) of use

HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment and facilities for drug substances and drug (medicinal) products. It has also been used primarily in the pharmaceutical industry for evaluating process safety hazards. As is the case with HACCP, the output of a HAZOP analysis is a list of critical operations for risk management. This facilitates regular monitoring of critical points in the manufacturing process.

I.7 Preliminary Hazard Analysis (PHA)

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system. The tool consists of: 1) the identification of the possibilities that the risk event happens, 2) the qualitative evaluation of the extent of possible injury or damage to health that could result and 3) a relative ranking of the hazard using a combination of severity and likelihood of occurrence, and 4) the identification of possible remedial measures.

Potential area(s) of use

PHA might be useful when analysing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used. It can be used for product, process and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product. PHA is most commonly used early in the

development of a project when there is little information on design details or operating procedures; thus, it will often be a precursor to further studies. Typically, hazards identified in the PHA are further assessed with other risk management tools such as those in this section.

I.8 Risk ranking and filtering

Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. "Filters," in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

Potential area(s) of use

Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. Risk ranking is useful when management needs to evaluate both quantitatively-assessed and qualitatively-assessed risks within the same organizational framework.

I.9 Supporting statistical tools

Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making. A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided:

(i) Control charts, for example:
- Acceptance control charts (see ISO 7966)
- Control charts with arithmetic average and warning limits (see ISO 7873)
- Cumulative sum charts (see ISO 7871)
- Shewhart control charts (see ISO 8258)
- Weighted moving average

(ii) Design of experiments (DOE)

(iii) Histograms

(iv) Pareto charts

(v) Process capability analysis

Annex II: Potential applications for quality risk management

This annex is intended to identify potential uses of quality risk management principles and tools by industry and regulators. However, the selection of particular risk management tools is completely dependent upon specific facts and circumstances. These examples are provided for illustrative purposes and only suggest potential uses of quality risk management. This Annex is not intended to create any new expectations beyond the current regulatory requirements.

II.1 Quality risk management as part of integrated quality management

Documentation

To review current interpretations and application of regulatory expectations

To determine the desirability of and/or develop the content for SOPs, guidelines, etc.

Training and education

To determine the appropriateness of initial and/or ongoing training sessions based on education, experience and working habits of staff, as well as on a periodic assessment of previous training (e.g., its effectiveness)

To identify the training, experience, qualifications and physical abilities allowing personnel to perform an operation reliably and with no adverse impact on the quality of the product.

Quality defects

To provide the basis for identifying, evaluating, and communicating the potential quality impact of a suspected quality defect, complaint, trend, deviation, investigation, out of specification result, etc.

To facilitate risk communications and determine appropriate action to address significant product defects, in conjunction with regulatory authorities (e.g., recall).

Auditing/inspection

To define the frequency and scope of audits, both internal and external, taking into account factors such as:

- existing legal requirements;
- overall compliance status and history of the company or facility
- robustness of a company's quality risk management activities
- complexity of the site
- complexity of the manufacturing process
- complexity of the product and its therapeutic significance
- number and significance of quality defects (e.g. recall)
- results of previous audits/inspections;
- major changes of building, equipment, processes, key personnel
- experience with manufacturing of a product (e.g. frequency, volume, number of batches)
- test results of official control laboratories.

Periodic review

To select, evaluate and interpret trend results of data within the product quality review

To interpret monitoring data (e.g., to support an assessment of the appropriateness of revalidation or changes in sampling)

Change management/change control

To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing

To evaluate the impact of the changes on the availability of the finished product

To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process or technical transfers

To determine appropriate actions preceding the implementation of a change, e.g. additional testing, (re)qualification, (re)validation or communication with regulators

Continual improvement

To facilitate continual improvement in processes throughout the product lifecycle.

II.2 Quality risk management as part of regulatory operations

Inspection and assessment activities

To assist with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity (see "Auditing" section in Annex II.1)

To evaluate the significance of, for example, quality defects, potential recalls and inspectional findings

To determine the appropriateness and type of post-inspection regulatory follow-up

To evaluate information submitted by industry including pharmaceutical development information

To evaluate impact of proposed variations or changes

To identify risks which should be communicated between inspectors and assessors to facilitate better understanding of how risks can be or are controlled (e.g., parametric release, Process Analytical Technology (PAT)).

II.3 Quality risk management as part of development

Quality risk management as part of development

To design a quality product and its manufacturing process to consistently deliver the intended performance of the product (see ICH Q8).

To enhance knowledge of product performance over a wide range of material attributes (e.g. particle size distribution, moisture content, flow properties), processing options and process parameters.

To assess the critical attributes of raw materials, solvents, Active Pharmaceutical Ingredient (API) starting materials, APIs, excipients, or packaging materials.

To establish appropriate specifications, identify critical process parameters and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing).

To decrease variability of quality attributes:

- Reduce product and material defects
- Reduce manufacturing defects

To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer.

To make use of the "design space" concept (see ICH Q8).

II.4 Quality risk management for facilities, equipment and utilities

Design of facilities/equipment

To determine appropriate zones when designing buildings and facilities, e.g.,

- Flow of material and personnel;
- Minimize contamination;
- Pest control measures;
- Prevention of mix-ups;
- Open versus closed equipment;
- Clean rooms versus isolator technologies;
- Dedicated or segregated facilities/equipment.

To determine appropriate product contact materials for equipment and containers (e.g., selection of stainless steel grade, gaskets, lubricants)

To determine appropriate utilities (e.g., steam, gases, power source, compressed air, heating, ventilation and air conditioning (HVAC), water)

To determine appropriate preventive maintenance for associated equipment (e.g., inventory of necessary spare parts)

Hygiene aspects in facilities

To protect the product from environmental hazards, including chemical, microbiological, and physical hazards (e.g., determining appropriate clothing and gowning, hygiene concerns)

To protect the environment (e.g., personnel, potential for cross-contamination) from hazards related to the product being manufactured

Qualification of facility / Equipment / Utilities

To determine the scope and extent of qualification of facilities, buildings, and production equipment and/or laboratory instruments (including proper calibration methods)

Cleaning of equipment and environmental control

To differentiate efforts and decisions based on the intended use (e.g., multi- versus single- purpose, batch versus continuous production)

To determine acceptable (specified) cleaning validation limits

Calibration/preventive maintenance

To set appropriate calibration and maintenance schedules

Computerised systems and computer controlled equipment
To select the design of computer hardware and software (e.g., modular, structured, fault tolerance)
To determine the extent of validation, e.g..

- identification of critical performance parameters
- selection of the requirements and design
- code review
- the extent of testing and test methods
- reliability of electronic records and signatures

II.5 Quality risk management as part of materials management

Assessment and evaluation of suppliers and contract manufacturers
To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing, supplier quality agreements)

Starting material
To assess differences and possible quality risks associated with variability in starting materials (e.g., age, route of synthesis).

Use of materials
To determine whether it is appropriate to use material under quarantine (e.g., for further internal processing)
To determine appropriateness of reprocessing, reworking, use of returned goods

Storage, logistics and distribution conditions
To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design)
To determine the effect on product quality of discrepancies in storage or transport conditions (e.g. cold chain management) in conjunction with other ICH guidelines
To maintain infrastructure (e.g. capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance)
To provide information for ensuring the availability of pharmaceuticals (e.g., ranking risks to the supply chain).

II.6 Quality risk management as part of production

Validation
To identify the scope and extent of verification, qualification and validation activities (e.g. analytical methods, processes, equipment and cleaning methods)
To determine the extent for follow-up activities (e.g. sampling, monitoring and re-validation)
To distinguish between critical and non-critical process steps to facilitate design of a validation study

In-process sampling & testing
To evaluate the frequency and extent of in-process control testing (e.g. to justify reduced testing under conditions of proven control)
To evaluate and justify the use of process analytical technologies (PAT) in conjunction with parametric and real time release

Production planning
To determine appropriate production planning (e.g. dedicated, campaign and concurrent production process sequences).

II.7 Quality risk management as part of laboratory control and stability studies

Out of specification results
To identify potential root causes and corrective actions during the investigation of out of specification results

Retest period/expiration date
To evaluate adequacy of storage and testing of intermediates, excipients and starting materials

II.8 Quality risk management as part of packaging and labelling

Design of packages
To design the secondary package for the protection of primary packaged product (e.g., to ensure product authenticity, label legibility)

Selection of container closure system
To determine the critical parameters of the container closure system

Label controls
To design label control procedures based on the potential for mix-ups involving different product labels, including different versions of the same label

Pharmaceutical quality system (ICH Q10)
The harmonised tripartite guideline of the International Conference on Harmonisation (ICH)

Table of contents

1. Pharmaceutical quality system

1.1. Introduction

This document establishes a new ICH tripartite guideline describing a model for an effective quality management system for the pharmaceutical industry, referred to as the Pharmaceutical Quality System. Throughout this guideline, the term "pharmaceutical quality system" refers to the ICH Q10 model.

ICH Q10 describes one comprehensive model for an effective pharmaceutical quality system that is based on International Standards Organisation (ISO) quality concepts, includes applicable Good Manufacturing Practice (GMP) regulations and complements ICH Q8 "Pharmaceutical Development" and ICH Q9 "Quality Risk Management". ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle. Much of the content of ICH Q10 applicable to manufacturing sites is currently specified by regional GMP requirements. ICH Q10 is not intended to create any new expectations beyond current regulatory requirements. Consequently, the content of ICH Q10 that is additional to current regional GMP requirements is optional.

ICH Q10 demonstrates industry and regulatory authorities' support of an effective pharmaceutical quality system to enhance the quality and availability of medicines around the world in the interest of public health. Implementation of ICH Q10 throughout the product lifecycle should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities.

1.2. Scope

This guideline applies to the systems supporting the development and manufacture of pharmaceutical drug substances (i.e., API) and drug products, including biotechnology and biological products, throughout the product lifecycle.

The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognising the differences among, and the different goals of each stage (see Section 3).

For the purposes of this guideline, the product lifecycle includes the following technical activities for new and existing products:

- Pharmaceutical development;
  - Drug substance development;
  - Formulation development (including container/closure system);
  - Manufacture of investigational products;
  - Delivery system development (where relevant);
  - Manufacturing process development and scale-up;
  - Analytical method development.
- Technology transfer
  - New product transfers during development through manufacturing;
  - Transfers within or between manufacturing and testing sites for marketed products.
- Commercial manufacturing
  - Acquisition and control of materials;
  - Provision of facilities, utilities and equipment;
  - Production (including packaging and labelling);
  - Quality control and assurance;
  - Release;
  - Storage;
  - Distribution (excluding wholesale activities).
- Product discontinuation
  - Retention of documentation;
  - Sample retention;
  - Continued product assessment and reporting.

1.3. Relationship of ICH Q10 to regional GMP requirements, ISO standards and ICH Q7

Regional GMP requirements, the ICH Q7 Guideline, "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients", and ISO quality management system guidelines form the foundation for ICH Q10. To meet the objectives described below, ICH Q10 augments GMP by describing specific quality system elements and management responsibilities. ICH Q10 provides a harmonised model for a pharmaceutical quality system throughout the lifecycle of a product and is intended to be used together with regional GMP requirements.

The regional GMPs do not explicitly address all stages of the product lifecycle (e.g., Development). The quality system elements and management responsibilities described in this guideline are intended to encourage the use of science and risk based approaches at each lifecycle stage, thereby promoting continual improvement across the entire product lifecycle.

1.4. Relationship of ICH Q10 to regulatory approaches

Regulatory approaches for a specific product or manufacturing facility should be commensurate with the level of product and process understanding, the results of quality risk management, and the effectiveness of the pharmaceutical quality system. When implemented, the effectiveness of the pharmaceutical quality system can normally be evaluated during a regulatory inspection at the manufacturing site. Potential opportunities to enhance science and risk based regulatory approaches are identified in Annex 1. Regulatory processes will be determined by region.

1.5. ICH Q10 objectives

Implementation of the Q10 model should result in achievement of three main objectives which complement or enhance regional GMP requirements.

1.5.1. Achieve product realisation

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

1.5.2. Establish and maintain a state of control

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

1.5.3. Facilitate continual improvement

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

1.6. Enablers: knowledge management and quality risk management

Use of knowledge management and quality risk management will enable a company to implement ICH Q10 effectively and successfully. These enablers will facilitate achievement of the objectives described in Section 1.5 above by providing the means for science and risk based decisions related to product quality.

1.6.1. Knowledge management

Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation. For example, development activities using scientific approaches provide knowledge for product and process understanding. Knowledge management is a systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components. Sources of knowledge include, but are not limited to prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process

validation studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and change management activities.

1.6.2. Quality risk management

Quality risk management is integral to an effective pharmaceutical quality system. It can provide a proactive approach to identifying, scientifically evaluating and controlling potential risks to quality. It facilitates continual improvement of process performance and product quality throughout the product lifecycle. ICH Q9 provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality.

1.7. Design and content considerations

(a) The design, organisation and documentation of the pharmaceutical quality system should be well structured and clear to facilitate common understanding and consistent application.

(b) The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognising the different goals and knowledge available for each stage.

(c) 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 pharmaceutical quality system should incorporate appropriate risk management principles. While some aspects of the pharmaceutical quality system can be company-wide and others site-specific, the effectiveness of the pharmaceutical quality system is normally demonstrated at the site level.

(d) The pharmaceutical quality system should include appropriate processes, resources and responsibilities to provide assurance of the quality of outsourced activities and purchased materials as described in Section 2.7.

(e) Management responsibilities, as described in Section 2, should be identified within the pharmaceutical quality system.

(f) The pharmaceutical quality system should include the following elements, as described in Section 3: process performance and product quality monitoring, corrective and preventive action, change management and management review.

(g) Performance indicators, as described in Section 4, should be identified and used to monitor the effectiveness of processes within the pharmaceutical quality system.

1.8. Quality manual

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

(a) The quality policy (see Section 2);

(b) The scope of the pharmaceutical quality system;

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

(d) Management responsibilities within the pharmaceutical quality system (see Section 2).

2. Management responsibility

Leadership is essential to establish and maintain a company-wide commitment to quality and for the performance of the pharmaceutical quality system.

2.1. Management commitment

(a) Senior management has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the quality objectives, and those roles, responsibilities, and authorities are defined, communicated and implemented throughout the company.

(b) Management should:

(1) Participate in the design, implementation, monitoring and maintenance of an effective pharmaceutical quality system;

(2) Demonstrate strong and visible support for the pharmaceutical quality system and ensure its implementation throughout their organisation;

(3) Ensure a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management;

(4) Define individual and collective roles, responsibilities, authorities and inter-relationships of all organisational units related to the pharmaceutical quality system. Ensure these interactions are communicated and understood at all levels of the organisation. An independent quality unit/structure with authority to fulfil certain pharmaceutical quality system responsibilities is required by regional regulations;

(5) Conduct management reviews of process performance and product quality and of the pharmaceutical quality system;

(6) Advocate continual improvement;

(7) Commit appropriate resources.

2.2. Quality policy

(a) Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality.

(b) The quality policy should include an expectation to comply with applicable regulatory requirements and should facilitate continual improvement of the pharmaceutical quality system.

(c) The quality policy should be communicated to and understood by personnel at all levels in the company.

(d) The quality policy should be reviewed periodically for continuing effectiveness.

2.3. Quality planning

(a) Senior management should ensure the quality objectives needed to implement the quality policy are defined and communicated.

(b) Quality objectives should be supported by all relevant levels of the company.

(c) Quality objectives should align with the company's strategies and be consistent with the quality policy.

(d) Management should provide the appropriate resources and training to achieve the quality objectives.

(e) Performance indicators that measure progress against quality objectives should be established, monitored, communicated regularly and acted upon as appropriate as described in Section 4.1 of this document.

2.4. Resource management

(a) Management should determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the pharmaceutical quality system and continually improve its effectiveness.

(b) Management should ensure that resources are appropriately applied to a specific product, process or site.

2.5. Internal communication

(a) Management should ensure appropriate communication processes are established and implemented within the organisation.

(b) Communications processes should ensure the flow of appropriate information between all levels of the company.

(c) Communication processes should ensure the appropriate and timely escalation of certain product quality and pharmaceutical quality system issues.

2.6. Management review

(a) Senior management should be responsible for pharmaceutical quality system governance through management review to ensure its continuing suitability and effectiveness.

(b) Management should assess the conclusions of periodic reviews of process performance and product quality and of the pharmaceutical quality system, as described in Sections 3 and 4.

2.7. Management of outsourced activities and purchased materials

The pharmaceutical quality system, including the management responsibilities described in this section, extends to the control and review of any outsourced activities and quality of purchased materials. The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials. These processes should incorporate quality risk management and include:

(a) Assessing prior to outsourcing operations or selecting material suppliers, the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (e.g., audits, material evaluations, qualification);

(b) Defining the responsibilities and communication processes for quality-related activities of the involved parties. For outsourced activities, this should be included in a written agreement between the contract giver and contract acceptor;

(c) Monitoring and review of the performance of the contract acceptor or the quality of the material from the provider, and the identification and implementation of any needed improvements;

(d) Monitoring incoming ingredients and materials to ensure they are from approved sources using the agreed supply chain.

2.8. Management of change in product ownership

When product ownership changes, (e.g., through acquisitions) management should consider the complexity of this and ensure:

(a) The ongoing responsibilities are defined for each company involved;

(b) The necessary information is transferred.

3. Continual improvement of process performance and product quality

This section describes the lifecycle stage goals and the four specific pharmaceutical quality system elements that augment regional requirements to achieve the ICH Q10 objectives, as defined in Section 1.5. It does not restate all regional GMP requirements.

3.1 Lifecycle stage goals

The goals of each product lifecycle stage are described below.

3.1.1. Pharmaceutical development

The goal of pharmaceutical development activities is to design a product and its manufacturing process to consistently deliver the intended performance and meet the needs of patients and healthcare professionals, and regulatory authorities and internal customers' requirements. Approaches to pharmaceutical development are described in ICH Q8. The results of exploratory and clinical development studies, while outside the scope of this guidance, are inputs to pharmaceutical development.

3.1.2. Technology transfer

The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation. This knowledge forms the basis for the manufacturing process, control strategy, process validation approach and ongoing continual improvement.

3.1.3. Commercial manufacturing

The goals of manufacturing activities include achieving product realisation, establishing and maintaining a state of control and facilitating continual improvement. The pharmaceutical quality system should assure that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded.

3.1.4. Product discontinuation

The goal of product discontinuation activities is to manage the terminal stage of the product lifecycle effectively. For product discontinuation, a pre-defined approach should be used to

manage activities such as retention of documentation and samples and continued product assessment (e.g., complaint handling and stability) and reporting in accordance with regulatory requirements.

3.2. Pharmaceutical quality system elements

The elements described below might be, required in part under regional GMP regulations. However, the Q10 model's intent is to enhance these elements in order to promote the lifecycle approach to product quality. These four elements are:

- Process performance and product quality monitoring system;
- Corrective action and preventive action (CAPA) system;
- Change management system;
- Management review of process performance and product quality.

These elements should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognising the differences among, and the different goals of, each stage. Throughout the product lifecycle, companies are encouraged to evaluate opportunities for innovative approaches to improve product quality.

Each element is followed by a table of example applications of the element to the stages of the pharmaceutical lifecycle.

3.2.1. Process performance and product quality monitoring system

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

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

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

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

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

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

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

Table I: Application of process performance and product quality monitoring system throughout the product lifecycle

Pharmaceutical development	Technology transfer	Commercial manufacturing	Product discontinuation
Process and product knowledge generated and process and product monitoring conducted throughout development can be used to establish a	Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing.	A well-defined system for process performance and product quality monitoring should be applied to assure performance within a	Once manufacturing ceases, monitoring such as stability testing should continue to completion of the studies. Appropriate action on marketed

control strategy for manufacturing.	Knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy.	state of control and to identify improvement areas.	product should continue to be executed according to regional regulations.

3.2.2. Corrective Action and Preventive Action (CAPA) system

The pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring. A structured approach to the investigation process should be used with the objective of determining the root cause. The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk, in line with ICH Q9. CAPA methodology should result in product and process improvements and enhanced product and process understanding.

Table II: Application of corrective action and preventive action system throughout the product lifecycle

Pharmaceutical development	Technology transfer	Commercial manufacturing	Product discontinuation
Product or process variability is explored. CAPA methodology is useful where corrective actions and preventive actions are incorporated into the iterative design and development process.	CAPA can be used as an effective system for feedback, feed-forward and continual improvement.	CAPA should be used and the effectiveness of the actions should be evaluated.	CAPA should continue after the product is discontinued. The impact on product remaining on the market should be considered as well as other products which might be impacted.

3.2.3. Change management system

Innovation, continual improvement, the outputs of process performance and product quality monitoring and CAPA drive change. In order to evaluate, approve and implement these changes properly, a company should have an effective change management system. There is generally a difference in formality of change management processes prior to the initial regulatory submission and after submission, where changes to the regulatory filing might be required under regional requirements.

The change management system ensures continual improvement is undertaken in a timely and effective manner. It should provide a high degree of assurance there are no unintended consequences of the change.

The change management system should include the following, as appropriate for the stage of the lifecycle:

(a) Quality risk management should be utilised to evaluate proposed changes. The level of effort and formality of the evaluation should be commensurate with the level of risk;

(b) Proposed changes should be evaluated relative to the marketing authorisation, including design space, where established, and/or current product and process understanding. There should be an assessment to determine whether a change to the regulatory filing is required under regional requirements. As stated in ICH Q8, working

within the design space is not considered a change (from a regulatory filing perspective). However, from a pharmaceutical quality system standpoint, all changes should be evaluated by a company's change management system;

(c) Proposed changes should be evaluated by expert teams contributing the appropriate expertise and knowledge from relevant areas (e.g., Pharmaceutical Development, Manufacturing, Quality, Regulatory Affairs and Medical), to ensure the change is technically justified. Prospective evaluation criteria for a proposed change should be set;

(d) After implementation, an evaluation of the change should be undertaken to confirm the change objectives were achieved and that there was no deleterious impact on product quality.

Pharmaceutical development	**Technology transfer**	**Commercial manufacturing**	**Product discontinuation**
Change is an inherent part of the development process and should be documented; the formality of the change management process should be consistent with the stage of pharmaceutical development.	The change management system should provide management and documentation of adjustments made to the process during technology transfer activities.	A formal change management system should be in place for commercial manufacturing. Oversight by the quality unit should provide assurance of appropriate science and risk based assessments.	Any changes after product discontinuation should go through an appropriate change management system.

3.2.4. Management review of process performance and product quality

Management review should provide assurance that process performance and product quality are managed over the entire lifecycle. Depending on the size and complexity of the company, management review can be a series of reviews at various levels of management and should include a timely and effective communication and escalation process to raise appropriate quality issues to senior levels of management for review.

(a) The management review system should include:
    (1) The results of regulatory inspections and findings, audits and other assessments, and commitments made to regulatory authorities;
    (2) Periodic quality reviews, that can include:
        i. Measures of customer satisfaction such as product quality complaints and recalls;
        ii. Conclusions of process performance and product quality monitoring;
        iii. The effectiveness of process and product changes including those arising from corrective action and preventive actions.
    (3) Any follow-up actions from previous management reviews.

(b) The management review system should identify appropriate actions, such as:
    (1) Improvements to manufacturing process and products;
    (2) Provision, training and/or realignment of resources;
    (3) Capture and dissemination of knowledge.

Table IV: Application of management review of process performance and product quality throughout the product lifecycle

Pharmaceutical development	**Technology transfer**	**Commercial manufacturing**	**Product discontinuation**

Aspects of management review can be performed to ensure adequacy of the product and process design.	Aspects of management review should be performed to ensure the developed product and process can be manufactured at commercial scale	Management review should be a structured system, as described above, and should support continual improvement	Management review should include such items as product stability and product quality complaints

4. Continual improvement of the pharmaceutical quality system

This section describes activities that should be conducted to manage and continually improve the pharmaceutical quality system.

4.1. Management review of the pharmaceutical quality system

Management should have a formal process for reviewing the pharmaceutical quality system on a periodic basis. The review should include:

(a) Measurement of achievement of pharmaceutical quality system objectives;

(b) Assessment of performance indicators that can be used to monitor the effectiveness of processes within the pharmaceutical quality system, such as:

(1) Complaint, deviation, CAPA and change management processes;

(2) Feedback on outsourced activities;

(3) Self-assessment processes including risk assessment, trending, and audits;

(4) External assessments such as regulatory inspections and findings and customer audits.

4.2. Monitoring of internal and external factors impacting the pharmaceutical quality system

Factors monitored by management can include:

(a) Emerging regulations, guidance and quality issues that can impact the Pharmaceutical Quality System;

(b) Innovations that might enhance the pharmaceutical quality system;

(c) Changes in product ownership.

4.3. Outcomes of management review and monitoring

The outcome of management review of the pharmaceutical quality system and monitoring of internal and external factors can include:

(a) Improvements to the pharmaceutical quality system and related processes;

(b) Allocation or reallocation of resources and/or personnel training;

(c) Revisions to quality policy and quality objectives;

(d) Documentation and timely and effective communication of the results of the management review and actions, including escalation of appropriate issues to senior management.

5. Glossary

ICH and ISO definitions are used in ICH Q10 where they exist. For the purpose of ICH Q10, where the words “requirement”, “requirements” or “necessary” appear in an ISO definition, they do not necessarily reflect a regulatory requirement. The source of the definition is identified in parentheses after the definition. Where no appropriate ICH or ISO definition was available, an ICH Q10 definition was developed.

Capability of a process:
Ability of a process to realise a product that will fulfil the requirements of that product. The concept of process capability can also be defined in statistical terms. (ISO 9000:2005)

Change management:
A systematic approach to proposing, evaluating, approving, implementing and reviewing changes. (ICH Q10)

Continual improvement:
Recurring activity to increase the ability to fulfil requirements. (ISO 9000:2005)

Control strategy
A planned set of controls, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Corrective action:
Action to eliminate the cause of a detected non-conformity or other undesirable situation. Note: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence. (ISO 9000:2005)

Design space:
The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. (ICH Q8)

Enabler:
A tool or process which provides the means to achieve an objective. (ICH Q10)

Feedback/Feed-forward:
Feedback: The modification or control of a process or system by its results or effects.
Feed-forward: The modification or control of a process using its anticipated results or effects. (Oxford Dictionary of English by Oxford University Press, 2003)
Feedback/feed-forward can be applied technically in process control strategies and conceptually in quality management. (ICH Q10)

Innovation:
The introduction of new technologies and methodologies. (ICH Q10)

Knowledge management:
Systematic approach to acquiring, analysis, storing and disseminating information related to products, manufacturing processes and components. (ICH Q10)

Outsourced activities:
Activities conducted by a contract acceptor under a written agreement with a contract giver. (ICH Q10)

Performance indicators:
Measurable values used to quantify quality objectives to reflect the performance of an organisation, process or system, also known as "performance metrics" in some regions. (ICH Q10)

Pharmaceutical Quality System (PQS):
Management system to direct and control a pharmaceutical company with regard to quality (ICH Q10 based upon ISO 9000:2005)

Preventive action:
Action to eliminate the cause of a potential non-conformity or other undesirable potential situation. Note: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence. (ISO 9000:2005)

Product realisation:
Achievement of a product with the quality attributes appropriate to meet the needs of patients, healthcare professionals, and regulatory authorities (including compliance with marketing authorisation) and internal customers' requirements. (ICH Q10)

Quality:

The degree to which a set of inherent properties of a product, system or process fulfils requirements. (ICH Q9)

Quality manual:
Document specifying the quality management system of an organisation. (ISO 9000:2005)

Quality objectives:
A means to translate the quality policy and strategies into measurable activities. (ICH Q10)

Quality planning:
Part of quality management focused on setting quality objectives and specifying necessary operational processes and related resources to fulfil the quality objectives. (ISO 9000:2005)

Quality policy:
Overall intentions and direction of an organisation related to quality as formally expressed by senior management. (ISO 9000:2005)

Quality risk management:
A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. (ICH Q9)

Senior management:
Person(s) who direct and control a company or site at the highest levels with the authority and responsibility to mobilise resources within the company or site. (ICH Q10 based in part on ISO 9000:2005)

State of control:
A condition in which the set of controls consistently provides assurance of continued process performance and product quality. (ICH Q10)

ANNEX 1

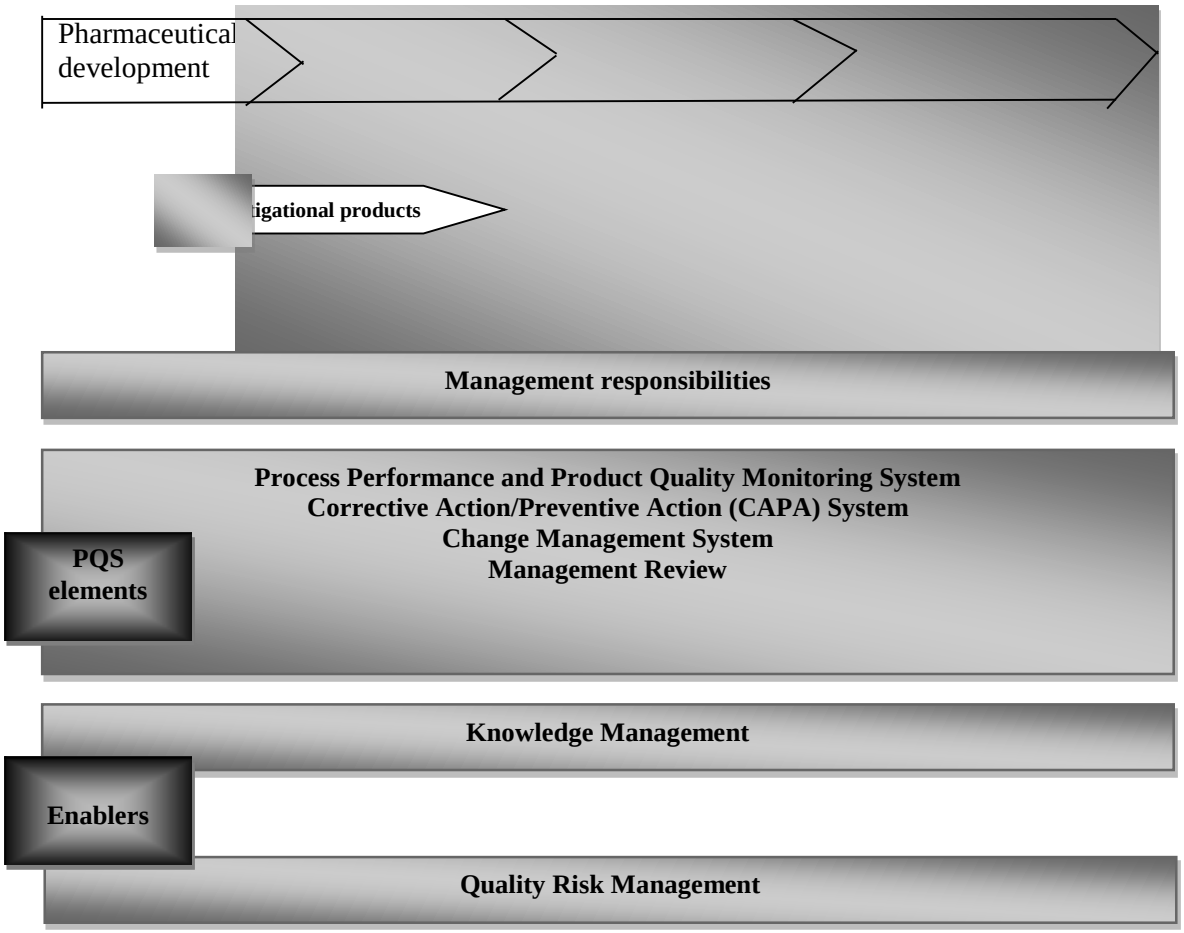
Potential opportunities to enhance science and risk based regulatory approaches*

Note: This annex reflects potential opportunities to enhance regulatory approaches. The actual regulatory process will be determined by region.

Scenario	Potential opportunity
1. Comply with GMPs	Compliance – status-quo
2. Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g. ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk based approaches for regulatory inspections.
3. Demonstrate product and process understanding, including effective use of quality risk management principles (e.g. ICH Q8 and ICH Q9).	Opportunity to: • facilitate science based pharmaceutical quality assessment; • enable innovative approaches to process validation; • establish real-time release mechanisms.
4. Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g. ICH Q8, ICH Q9 and ICH Q10).	Opportunity to: • increase use of risk based approaches for regulatory inspections; • facilitate science based pharmaceutical quality assessment; • optimise science and risk based post-approval change processes to maximise benefits from innovation and continual improvement; • enable innovative approaches to process validation; • establish real-time release mechanisms.

ANNEX 2

Diagram of the ICH Q10 Pharmaceutical Quality System Model



This diagram illustrates the major features of the ICH Q10 Pharmaceutical Quality System (PQS) model. The PQS covers the entire lifecycle of a product including pharmaceutical development, technology transfer, commercial manufacturing, and product discontinuation as illustrated by the upper portion of the diagram. The PQS augments regional GMPs as illustrated in the diagram. The diagram also illustrates that regional GMPs apply to the manufacture of investigational medicinal products.

The next horizontal bar illustrates the importance of management responsibilities explained in Section 2 to all stages of the product lifecycle. The following horizontal bar lists the PQS elements which serve as the major pillars under the PQS model. These elements should be applied appropriately and proportionally to each lifecycle stage recognising opportunities to identify areas for continual improvement.

The bottom set of horizontal bars illustrates the enablers: knowledge management and quality risk management, which are applicable throughout the lifecycle stages. These enablers support the PQS goals of achieving product realisation, establishing and maintaining a state of control, and facilitating continual improvement.

Content of the batch certificate for a medicinal product exported by a manufacturer in a certain country based on a Mutual Recognition Agreement (MRA)

In the framework of Mutual Recognition Agreements (MRA), the Sectoral Annex on Good Manufacturing Practices (GMP) requires a batch certification scheme for medicinal products covered by the pharmaceutical annex. Batch certification is also required in the Agreements on Conformity Assessment and Acceptance of Industrial Products (ACAA) and other appropriate arrangements on GMP between third countries and the European Union (EU).

The internationally harmonised requirements for the content of the batch certificate of a medicinal product are provided in this document.

Each batch of medicinal product transferred between countries having appropriate arrangements on GMP, must be accompanied by a batch certificate issued by the manufacturer in the exporting country. In the framework of MRAs all manufacturing sites must be located in the country issuing the certificate or in another MRA country, if reciprocal arrangements are in force. In the framework of the European Union's ACAA with Israel (once in operation) all quality control sites must be located in Israel or the EU.

This certificate will be issued further to a full qualitative and quantitative analysis of all active and other relevant constituents to ensure that the quality of the products complies with the requirements of the marketing authorisation of the importing country. The batch certificate will attest that the batch meets the specifications and has been manufactured in accordance with the marketing authorisation of the importing country, detailing the specifications of the product, the analytical methods referenced, the analytical results obtained, and containing a statement that the batch processing, packaging and quality control records were reviewed and found in conformity with GMP. The batch certificate will be signed by the person responsible for certifying that the batch is suitable for release for sale or supply/export.

The importer/site of batch release of the medicinal product is to receive and maintain the batch certificate issued by the manufacturer of the exporting country. Upon request, it has to be readily available to the staff of the regulatory authorities of the importing country. This certification by the manufacturer on the conformity of each batch is essential to exempt the importer/site of batch release from re-control (see Art. 760 (2) of Law No. 95/2006, Title XVII).

Where applicable this batch certificate shall also be used for non-finished medicinal products such as intermediates, bulk or partially packed products.

This certificate may also be used for active pharmaceutical ingredients and investigational medicinal products used in clinical trial authorisations. The terminology may need to be adapted as per the Glossary.

These harmonised requirements have been agreed bilaterally by the European Union with the regulatory authorities of the following countries: Australia, Canada, Israel, Japan, New Zealand and Switzerland.

CONTENT OF THE BATCH CERTIFICATE FOR A MEDICINAL PRODUCT EXPORTED BY A MANUFACTURER IN A CERTAIN COUNTRY BASED ON A MUTUAL RECONGNITION AGREEMENT (MRA)

[Letter head of exporting manufacturer]

1. Name of product.
Trade name in importing country.

2. Importing country.

3. Marketing Authorisation Number.
The marketing authorisation number of the product in the importing country.

4. Strength/potency.
Identity (name) and amount per unit dose required for all active ingredients/constituents.

5. Dosage form (pharmaceutical form).

6. Package size (contents of container) and **type** (e.g. vials, bottles, blisters).

7. Batch number/Lot number.
For each product.

8. Date of manufacture.
In accordance with national (local) requirements.

9. Expiry date.
The date placed on the container/label of a product designating the time during which the product is expected to remain within the authorised shelf life specifications authorised by the importing country, if stored under defined conditions, and after which it should not be used.

10. Name and address of the manufacturer(s) – manufacturing site(s).
All sites involved in the manufacture including packaging/labelling and quality control of the batch should be listed with name, address and authorisation number. The name and address must correspond to the information provided on the manufacturing authorisation.

11. Number of the manufacturing authorisation/GMP certificate of the manufacturer.
The number should be provided for each site listed in Section 10.

12. Results of analysis.
Should include the authorised specifications, all results obtained and refer to the methods used (may refer to a separate certificate of analysis which must be dated, signed and attached).

13. Comments/remarks.
Any additional information that can be of value to the importer and/or inspector verifying the compliance of the batch certificate (e.g. specific storage or transportation conditions).

14. Certification statement.
This statement should cover the fabrication/manufacturing, including packaging/labelling and quality control. The following text should be used: ”I hereby certify that the above information is authentic and accurate. This batch of product has been manufactured, including packaging/labelling and quality control at the above mentioned site(s) in full compliance with the GMP requirements of the local Regulatory Authority and with the specifications in the Marketing Authorisation of the importing country or product specification file for Investigational Medicinal Products. The batch processing, packaging and analysis records were reviewed and found to be in compliance with GMP”.

15. Name and position/title of person authorising the batch release.
Including the name and address, if more than one site is mentioned under item 10.

16. Signature of person authorising the batch release.

17. Date of signature.

ANNEX 1

MANUFACTURE OF STERILE MEDICINAL PRODUCTS

Principle

The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance is particularly important, and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedures. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test.

Note: This Annex does not lay down detailed methods for determining the microbiological and particulate cleanliness of air, surfaces etc. Reference must be made to other documents such as the EN/ISO Standards.

General

1. The manufacture of sterile products must be carried out in clean areas entry to which must be through airlocks for personnel and/or for equipment and materials. Clean areas must be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.

2. The various operations of component preparation, product preparation and filling must be carried out in separate areas within the clean area. Manufacturing operations are divided into two categories; firstly those where the product is terminally sterilised, and secondly those which are conducted aseptically at some or all stages.

3. Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the "operational state" in order to minimise the risks of particulate or microbial contamination of the product or materials being handled.
In order to meet "in operation" conditions these areas must be designed to reach certain specified air-cleanliness levels in the "at rest" occupancy state. The "at-rest" state is the condition where the installation is installed and operating, complete with production equipment but with no operating personnel present. The "in operation" state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.

   The "in operation" and "at rest" states must be defined for each clean room or suite of clean rooms.

   For the manufacture of sterile medicinal products 4 grades can be distinguished.

   Grade A: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems must provide a homogeneous

air speed in a range of 0.36 – 0.54 m/s (guidance value) at the working position in open clean room applications.

The maintenance of laminarity must be demonstrated and validated.

A uni-directional air flow and lower velocities may be used in closed isolators and glove boxes.

Grade B: For aseptic preparation and filling, Grade B is the background environment for the Grade A zone.

Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

Clean room and clean air device classification

4. Clean rooms and clean air devices must be classified in accordance with EN ISO 14644-1. Classification must be clearly differentiated from operational process environmental monitoring. The maximum permitted airborne particle concentration for each grade is given in the following table.

	Maximum permitted number of particles per m^3 equal to or greater than the tabulated size			
Grade	**At rest**		**In operation**	
	0.5 μm	5 μm	0.5 μm	5 μm
A	3 520	20	3 520	20
B	3 520	29	352 000	2 900
C	352 000	2 900	3 520 000	29 000
D	3 520 000	29 000	indefinite	indefinite

5. For classification purposes in Grade A zones, a minimum sample volume of $1m^3$ must be taken per sample location. For Grade A the airborne particle classification is ISO 4.8 dictated by the limit for particles ≥5.0 μm. For Grade B (at rest) the airborne particle classification is ISO 5 for both considered particle sizes. For Grade C (at rest and in operation) the airborne particle classification is ISO 7 and ISO 8 respectively. For Grade D (at rest) the airborne particle classification is ISO 8. For classification purposes EN/ISO 14644-1 methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size and the method of evaluation of the data collected.

6. Portable particle counters with a short length of sample tubing must be used for classification purposes because of the relatively higher rate of precipitation of particles ≥5.0μm in remote sampling systems with long lengths of tubing. Isokinetic sample heads shall be used in unidirectional airflow systems.

7. "In operation" classification may be demonstrated during normal operations, simulated operations or during media fills as worst-case simulation is required for this. EN ISO 14644-2 provides information on testing to demonstrate continued compliance with the assigned cleanliness classifications.

Clean room and clean air device monitoring

8. Clean rooms and clean air devices must be routinely monitored in operation and the monitoring locations based on a formal risk analysis study and the results obtained during the classification of rooms and/or clean air devices.

9. For Grade A zones, particle monitoring must be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g. live organisms and radiological hazards. In such cases monitoring during routine equipment set up operations

must be undertaken prior to exposure to the risk. Monitoring during simulated operations must also be performed. The Grade A zone must be monitored at such a frequency and with suitable sample size that all interventions, transient events and any system deterioration would be captured and alarms triggered if alert limits are exceeded. It is accepted that it may not always be possible to demonstrate low levels of ≥5.0 μm particles at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

10. It is recommended that a similar system be used for Grade B zones although the sample frequency may be decreased. The importance of the particle monitoring system must be determined by the effectiveness of the segregation between the adjacent Grade A and B zones. The Grade B zone must be monitored at such a frequency and with suitable sample size that changes in levels of contamination and any system deterioration would be captured and alarms triggered if alert limits are exceeded.

11. Airborne particle monitoring systems may consist of independent particle counters; a network of sequentially accessed sampling points connected by manifold to a single particle counter; or a combination of the two. The system selected must be appropriate for the particle size considered. Where remote sampling systems are used, the length of tubing and the radii of any bends in the tubing must be considered in the context of particle losses in the tubing. The selection of the monitoring system must take account of any risk presented by the materials used in the manufacturing operation, for example those involving live organisms or radiopharmaceuticals.

12. The sample sizes taken for monitoring purposes using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of clean rooms and clean air devices.

13. In Grade A and B zones, the monitoring of the ≥5.0 μm particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure. The occasional indication of ≥5.0 μm particle counts may be false counts due to electronic noise, stray light, coincidence, etc. However consecutive or regular counting of low levels is an indicator of a possible contamination event and must be investigated. Such events may indicate early failure of the HVAC system, filling equipment failure or may also be diagnostic of poor practices during machine set-up and routine operation.

14. The particle limits given in the table for the "at rest" state must be achieved after a short "clean up" period of 15-20 minutes (guidance value) in an unmanned state after completion of operations.

15. The monitoring of Grade C and D areas in operation must be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended "clean up period" must be attained.

16. Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters must not interfere with the defined cleanliness standards.

17. Examples of operations to be carried out in the various grades are given in the table below (see also paragraphs 28 to 35):

Grade	**Examples of operations for terminally sterilised products (see paragraphs 28-30)**
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Grade	Examples of operations for aseptic preparations (see paragraphs 31-35)
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

18. Where aseptic operations are performed monitoring must be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation must not interfere with zone protection. Results from monitoring must be considered when reviewing batch documentation for finished product release. Surfaces and personnel must be monitored after critical operations.

Additional microbiological monitoring is also required outside production operations, e.g. after validation of systems, cleaning and sanitisation.

19. Recommended limits for microbiological monitoring of clean areas during operation:

Recommended limits for microbial contamination [a]				
Grade	**Air sample cfu*/m^3**	**Settle plates (diameter 90 mm) cfu*/4 hours [b]**	**Contact plates (diameter 55 mm) cfu*/plate**	**Glove print 5 fingers cfu*/glove**
A	< 1	< 1	< l	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

*c.f.u.= colony-forming units

Notes: [a] these are average values;

[b] Individual settle plates may be exposed for less than 4 hours.

20. Appropriate alert and action limits must be set for the results of particulate and microbiological monitoring. If these limits are exceeded standard operating procedures must prescribe corrective action.

Isolator technologies

20. The utilisation of isolator technology to minimize human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment must be designed so that the required air quality for the respective zones can be realised.
Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from a single door to double door designs to fully sealed systems incorporating sterilisation mechanisms.

22. The transfer of materials into and out of the unit is one of the greatest potential sources of contamination. In general the area inside the isolator is the local zone for high risk manipulations, although it is recognised that laminar air flow may not exist in the working zone of all such devices.

23. The air classification required for the background environment depends on the design of the isolator and its application. It must be controlled and for aseptic processing it must be at least grade D.

24. Isolators must be introduced only after appropriate validation. Validation must take into account all critical factors of isolator technology, for example the quality of the air inside

and outside (background) the isolator, sanitisation of the isolator, the transfer process and isolator integrity.

25. Monitoring must be carried out routinely and must include frequent leak testing of the isolator and glove/sleeve system.

Blow/fill/seal technology

26. Blow/Fill/Seal units are purpose built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A/B clothing is used. The environment must comply with the viable and non-viable limits at rest and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products which are terminally sterilised must be installed in at least a grade D environment.

27. Because of this special technology, particular attention must be paid to at least the following:

    a. Equipment design and qualification
    b. Validation and reproducibility of cleaning-in-place and sterilisation-in-place
    c. Background clean room environment in which the equipment is located
    d. Operator training and clothing
    e. Interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

Terminally sterilized products

28. Preparation of components and most products must be done in at least a grade D environment in order to give low risk of microbial and particulate contamination, suitable for filtration and sterilisation. Where the product is at a high or unusual risk of microbial contamination, (e.g. because the product actively supports microbial growth or must be held for a long period before sterilisation or is necessarily processed not mainly in closed vessels), then preparation must be carried out in a grade C environment.

29. Filling of products for terminal sterilisation must be carried out in at least a grade C environment.

30. Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling must be done in a grade A zone with at least a grade C background. Preparation and filling of ointments, creams, suspensions and emulsions must generally be carried out in a grade C environment before terminal sterilisation.

Aseptic preparation

31. Components after washing must be handled in at least a grade D environment. Handling of sterile starting materials and components, unless subjected to sterilisation or filtration through a micro-organism-retaining filter later in the process, must be done in a grade A environment with grade B background.

32. Preparation of solutions which are to be sterile filtered during the process must be done in a grade C environment; if not filtered, the preparation of materials and products must be done in a grade A environment with a grade B background.

33. Handling and filling of aseptically prepared products must be done in a grade A environment with a grade B background.

34. Prior to the completion of stoppering, transfer of partially closed containers, as used in freeze drying must be done either in a grade A environment with grade B background or in sealed transfer trays in a grade B environment.
35. Preparation and filling of sterile ointments, creams, suspensions and emulsions must be done in a grade A environment, with a grade B background, when the product is exposed and is not subsequently filtered.

Personnel

36. Only the minimum number of personnel required must be present in clean areas; this is particularly important during aseptic processing. Inspections and controls must be conducted outside the clean areas as far as possible.
37. All personnel (including those concerned with cleaning and maintenance) employed in such areas must receive regular training in disciplines relevant to the correct manufacture of sterile products. This training must include reference to hygiene and to the basic elements of microbiology. When outside staff who have not received such training (e.g. building or maintenance contractors) need to be brought in, particular care must be taken over their instruction and supervision.
38. Staff who have been engaged in the processing of animal tissue materials or of cultures of micro-organisms other than those used in the current manufacturing process must not enter sterile-product areas unless rigorous and clearly defined entry procedures have been followed.
39. High standards of personal hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations must be instructed to report any condition which may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue microbiological hazard must be decided by a designated competent person.
40. Wristwatches, make-up and jewellery must not be worn in clean areas.
41. Changing and washing must follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas.
42. The clothing and its quality must be appropriate for the process and grade of the working area. It must be worn so as to protect the product from contamination.
43. The description of clothing required for each grade is given below:

    Grade D: Hair and, where relevant, beard must be covered. A general protective suit and appropriate shoes must be worn. Appropriate measures must be taken to prevent any contamination coming from outside the clean area.
    Grade C: Hair and where relevant beard and moustache must be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes must be worn. They must shed virtually no fibres or particulate matter.
    Grade A/B: Headgear must totally enclose hair and, where relevant, beard and moustache; it must be tucked into the neck of the suit; a face mask must be worn to prevent the shedding of droplets. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear must be worn. Trouser-legs must be tucked inside the footwear and garment sleeves into the gloves. The protective clothing must shed virtually no fibres or particulate matter and retain particles shed by the body.

44. Outdoor clothing must not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilised or adequately sanitised) protective garments must be provided at each work session. Gloves must be regularly

disinfected during operations. Masks and gloves must be changed at least for every working session.

45. Clean area clothing must be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. These operations must follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibres and may increase the risk of shedding of particles.

Premises

46. In clean areas, all exposed surfaces must be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or micro-organisms and to permit the repeated application of cleaning agents, and disinfectants where used.

47. To reduce accumulation of dust and to facilitate cleaning there must be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors must be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason.

48. False ceilings must be sealed to prevent contamination from the space above them.

49. Pipes and ducts and other utilities must be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.

50. Sinks and drains must be prohibited in grade A/B areas used for aseptic manufacture. In other areas air breaks must be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms must be fitted with traps or water seals to prevent backflow.

51. Changing rooms must be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They must be flushed effectively with filtered air. The final stage of the changing room must, in the at-rest state, be the same grade as the area into which it leads. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. In general hand washing facilities must be provided only in the first stage of the changing rooms.

52. Both airlock doors must not be opened simultaneously. An interlocking system or a visual and/or audible warning system must be operated to prevent the opening of more than one door at a time.

53. A filtered air supply must maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and must flush the area effectively. Adjacent rooms of different grades must have a pressure differential of 10 – 15 Pascal's (guidance values). Particular attention must be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations.

54. It must be demonstrated that air-flow patterns do not present a contamination risk, e.g. care must be taken to ensure that air flows do not distribute particles from a particle generating person, operation or machine to a zone of higher product risk.

55. A warning system must be provided to indicate failure in the air supply. Indicators of pressure differences must be fitted between areas where these differences are important. These pressure differences must be recorded regularly or otherwise documented.

Equipment

56. A conveyor belt must not pass through a partition between a grade A or B area and a processing area of lower air cleanliness, unless the belt itself is continually sterilised (e.g. in a sterilising tunnel).

57. As far as practicable equipment, fittings and services must be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilisation is required, it must be carried out, wherever possible, after complete reassembly.

58. When equipment maintenance has been carried out within the clean area, the area must be cleaned, disinfected and/or sterilised where appropriate, before processing recommences if the required standards of cleanliness and/or asepsis have not been maintained during the work.

59. Water treatment plants and distribution systems must be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They must not be operated beyond their designed capacity. Water for injections must be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70°C.

60. All equipment such as sterilisers, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems must be subject to validation and planned maintenance; their return to use must be approved.

Sanitation

61. The sanitation of clean areas is particularly important. They must be cleaned thoroughly in accordance with a written programme. Where disinfectants are used, more than one type must be employed. Monitoring must be undertaken regularly in order to detect the development of resistant strains.

62. Disinfectants and detergents must be regularly monitored for microbial contamination; dilutions must be kept in previously cleaned containers and must only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas must be sterile prior to use.

63. Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

Processing

64. Precautions to minimize contamination must be taken during all processing stages including the stages before sterilisation.

65. Preparations of microbiological origin must not be made or filled in areas used for the processing of other medicinal products; however, vaccines of dead organisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products.

66. Validation of aseptic processing must include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium must be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilisation of the nutrient medium.

67. The process simulation test must imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. It must also take into account various interventions known to occur during normal production as well as worst-case situations.

68. Process simulation tests must be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC-system, equipment, process and number of shifts. Normally process simulation tests must be repeated twice a year per shift and process.

69. The number of containers used for media fills must be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills must at least equal the size of the product batch. The target must be zero growth and the following must apply:
- when filling fewer than 5000 units, no contaminated unit must be detected.
- when filling 5000 to 10000 units:
    a) One (1) contaminated unit must result in an investigation, including consideration of a repeat media fill;
    b) Two (2) contaminated units are considered cause for revalidation, following investigation.
- when filling more than 10000 units:
    a) One (1) contaminated unit must result in an investigation;
    b) Two (2) contaminated units are considered cause for revalidation, following investigation.

70. For any run size, intermittent incidents of microbial contamination may be indicative of low-level contamination that must be investigated. Investigation of gross failures must include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.

71. Care must be taken that any validation does not compromise the processes.

72. Water sources, water treatment equipment and treated water must be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins. Records must be maintained of the results of the monitoring and of any action taken.

73. Activities in clean areas and especially when aseptic operations are in progress must be kept to a minimum and movement of personnel must be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity must not be uncomfortably high because of the nature of the garments worn.

74. Microbiological contamination of starting materials must be minimal. Specifications must include requirements for microbiological quality when the need for this has been indicated by monitoring.

75. Containers and materials liable to generate fibres must be minimised in clean areas.

76. Where appropriate, measures must be taken to minimize the particle contamination of the finished product.

77. Components, containers and equipment must be handled after the final cleaning process in such a way that they are not recontaminated.

78. The interval between the washing and drying and the sterilisation of components, containers and equipment as well as between their sterilisation and use must be minimised and subject to a time-limit appropriate to the storage conditions.

79. The time between the start of the preparation of a solution and its sterilisation or filtration through a micro-organism-retaining filter must be minimised. There must be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.

80. The bioburden must be monitored before sterilisation. There must be working limits on contamination immediately before sterilisation, which are related to the efficiency of the

method to be used. Bioburden assay must be performed on each batch for both aseptically filled product and terminally sterilised products. Where overkill sterilisation parameters are set for terminally sterilised products, bioburden might be monitored only at suitable scheduled intervals. For parametric release systems, bioburden assay must be performed on each batch and considered as an in-process test. Where appropriate the level of endotoxins must be monitored. All solutions, in particular large volume infusion fluids, must be passed through a micro-organism-retaining filter, if possible sited immediately before filling.

81. Components, containers, equipment and any other article required in a clean area where aseptic work takes place must be sterilised and passed into the area through double-ended sterilisers sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination. Non-combustible gases must be passed through micro-organism retentive filters.

82. The efficacy of any new procedure must be validated, and the validation verified at scheduled intervals based on performance history or when any significant change is made in the process or equipment.

Sterilisation

83. All sterilisation processes must be validated. Particular attention must be given when the adopted sterilisation method is not described in the current edition of the European Pharmacopoeia, or when it is used for a product which is not a simple aqueous or oily solution. Where possible, heat sterilisation is the method of choice. In any case, the sterilisation process must be in accordance with the marketing and manufacturing authorisations.

84. Before any sterilisation process is adopted its suitability for the product and its efficacy in achieving the desired sterilising conditions in all parts of each type of load to be processed must be demonstrated by physical measurements and by biological indicators where appropriate. The validity of the process must be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records must be kept of the results.

85. For effective sterilisation the entire material must be subjected to the required treatment and the process must be designed to ensure that this is achieved.

86. Validated loading patterns must be established for all sterilisation processes.

87. Biological indicators must be considered as an additional method for monitoring the sterilisation. They must be stored and used according to the manufacturer's instructions, and their quality checked by positive controls. If biological indicators are used, strict precautions must be taken to avoid transferring microbial contamination from them.

88. There must be a clear means of differentiating products which have not been sterilised from those which have. Each basket, tray or other carrier of products or components must be clearly labelled with the material name, its batch number and an indication of whether or not it has been sterilised. Indicators such as autoclave tape may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilisation process, but they do not give a reliable indication that the lot is, in fact, sterile.

89. Sterilisation records must be available for each sterilisation run. They must be approved as part of the batch release procedure.

Sterilisation by heat

90. Each heat sterilisation cycle must be recorded on a time/temperature chart with a sufficiently large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling and/or recording

must have been determined during the validation, and where applicable also checked against a second independent temperature probe located at the same position.

91. Chemical or biological indicators may also be used, but must not take the place of physical measurements.

92. Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilising time-period is commenced. This time must be determined for each type of load to be processed.

93. After the high temperature phase of a heat sterilisation cycle, precautions must be taken against contamination of a sterilised load during cooling. Any cooling fluid or gas in contact with the product must be sterilised unless it can be shown that any leaking container would not be approved for use.

Moist heat

94. Both temperature and pressure must be used to monitor the process. Control instrumentation must normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they must be validated to ensure that critical process requirements are met.
System and cycle faults must be registered by the system and observed by the operator. The reading of the independent temperature indicator must be routinely checked against the chart recorder during the sterilisation period. For sterilisers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position, throughout the sterilisation period. There must be frequent leak tests on the chamber when a vacuum phase is part of the cycle.

95. The items to be sterilised, other than products in sealed containers, must be wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilisation. All parts of the load must be in contact with the sterilizing agent at the required temperature for the required time.

96. Care must be taken to ensure that steam used for sterilisation is of suitable quality and does not contain additives at a level which could cause contamination of product or equipment.

Dry heat

97. The process used must include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted must be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins must be used as part of the validation.

Sterilisation by radiation

98. Radiation sterilisation is used mainly for the sterilisation of heat sensitive materials and products. Many medicinal products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the product has been confirmed experimentally. Ultraviolet irradiation is not normally an acceptable method of sterilisation.

99. During the sterilisation procedure the radiation dose must be measured. For this purpose, dosimetry indicators which are independent of dose rate must be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters must be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the irradiator. Where plastic dosimeters are used they must be used within the time-limit of their calibration. Dosimeter absorbances must be read within a short period after exposure to radiation.

100. Biological indicators may be used as an additional control.

101. Validation procedures must ensure that the effects of variations in density of the packages are considered.

102. Materials handling procedures must prevent mix-up between irradiated and non-irradiated materials. Radiation sensitive colour disks must also be used on each package to differentiate between packages which have been subjected to irradiation and those which have not.

103. The total radiation dose must be administered within a predetermined time span.

Sterilisation with ethylene oxide

104. This method must only be used when no other method is practicable. During process validation it must be shown that there is no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material.

105. Direct contact between gas and microbial cells is essential; precautions must be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.

106. Before exposure to the gas, materials must be brought into equilibrium with the humidity and temperature required by the process. The time required for this must be balanced against the opposing need to minimize the time before sterilisation.

107. Each sterilisation cycle must be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained must form part of the batch record.

108. For each sterilisation cycle, records must be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process and of the gas concentration and of the total amount of gas used. The pressure and temperature must be recorded throughout the cycle on a chart. The record(s) must form part of the batch record.

109. After sterilisation, the load must be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process must be validated.

Filtration of medicinal products which cannot be sterilised in their final container

110. Filtration alone is not considered sufficient when sterilisation in the final container is possible. With regard to methods currently available, steam sterilisation is to be preferred. If the product cannot be sterilised in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilised container. Such filters can remove most bacteria and moulds, but not all viruses or mycoplasmas. Consideration must be given to complementing the filtration process with some degree of heat treatment.

111. Due to the potential additional risks of the filtration method as compared with other sterilisation processes, a second filtration via a further sterilised micro-organism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration must be carried out as close as possible to the filling point.

112. Fibre-shedding characteristics of filters must be minimal.

113. The integrity of the sterilised filter must be verified before use and must be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure

difference to be used across the filter must be determined during validation and any significant differences from this during routine manufacturing must be noted and investigated. Results of these checks must be included in the batch record. The integrity of critical gas and air vent filters must be confirmed after use. The integrity of other filters must be confirmed at appropriate intervals.

114. The same filter must not be used for more than one working day unless such use has been validated.

115. The filter must not affect the product by removal of ingredients from it or by release of substances into it.

Finishing of sterile products

116. Partially stoppered freeze drying vials must be maintained under Grade A conditions at all times until the stopper is fully inserted.

117. Containers must be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules must be subject to 100% integrity testing. Samples from other containers must be checked for integrity according to appropriate procedures.

118. The container closure system for aseptically filled vials is not fully integral until the aluminium cap has been crimped into place on the stoppered vial. Crimping of the cap must therefore be performed as soon as possible after stopper insertion.

119. As the equipment used to crimp vial caps can generate large quantities of non-viable particulates, the equipment must be located at a separate station equipped with adequate air extraction.

120. Vial capping can be undertaken as an aseptic process using sterilised caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials must be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials must be protected with a Grade A air supply until the cap has been crimped.

121. Vials with missing or displaced stoppers must be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology must be used to prevent direct contact with the vials and to minimise microbial contamination.

122. Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimising direct human interventions into the capping operation.

123. Containers sealed under vacuum must be tested for maintenance of that vacuum after an appropriate, pre-determined period.

124. Filled containers of parenteral products must be inspected individually for extraneous contamination or other defects. When inspection is done visually, it must be done under suitable and controlled conditions of illumination and background. Operators doing the inspection must pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from inspection. Where other methods of inspection are used, the process must be validated and the performance of the equipment checked at intervals. Results must be recorded.

Quality control

125. The sterility test applied to the finished product must only be regarded as the last in a series of control measures by which sterility is assured. The test must be validated for the product(s) concerned.

126. In those cases where parametric release has been authorised, special attention must be paid to the validation and the monitoring of the entire manufacturing process.

127. Samples taken for sterility testing must be representative for the whole batch, but must in particular include samples taken from parts of the batch considered to be most at risk of contamination, e.g.:

a. for products which have been filled aseptically, samples must include containers filled at the beginning and end of the batch and after any significant intervention;

b. or products which have been heat sterilised in their final containers, consideration must be given to taking samples from the potentially coolest part of the load.

ANNEX 2

MANUFACTURE OF BIOLOGICAL MEDICINAL PRODUCTS FOR HUMAN USE

Scope

The methods employed in the manufacture of biological medicinal products are a critical factor in shaping the appropriate regulatory control. Biological medicinal products can be defined therefore largely by reference to their method of manufacture. Biological medicinal products prepared by the following methods of manufacture will fall under the scope of this annex[3]:

a) Microbial cultures, excluding those resulting from r-DNA techniques;
b) Microbial and cell cultures, including those resulting from recombinant DNA or hybridoma techniques;
c) Extraction from biological tissues;
d) Propagation of live agents in embryos of animals.

(Not all of the aspects of this Annex may necessarily apply to products in category a).

Note: In drawing up this Annex, due consideration has been given to the general requirements for manufacturing establishments and control laboratories proposed by the WHO.
This Annex does not lay down detailed requirements for specific classes of biological products, and attention is therefore directed to other guidelines issued by the Committee for Proprietary Medicinal Products (CPMP), for example the note for guidance on monoclonal antibodies and the note for guidance on products of recombinant DNA technology ("The rules governing medicinal product in the European Community", Volume 3).

Principle

The manufacture of biological medicinal products involves certain specific considerations arising from the nature of the products and the processes. The ways in which biological medicinal products are produced, controlled and administered make some particular precautions necessary.

Unlike conventional medicinal products, which are reproduced using chemical and physical techniques capable of a high degree of consistency, the production of biological medicinal products involves biological processes and materials, such as cultivation of cells or extraction of material from living organisms. These biological processes may display inherent variability, so

[3] Biological medicinal products manufactured by these methods include: vaccines, immunosera, antigens, hormones, cytokines, enzymes and other products of fermentation (including monoclonal antibodies and products derived from r-DNA).

that the range and nature of by-products are variable. Moreover, the materials used in these cultivation processes provide good substrates for growth of microbial contaminants.

The control of biological medicinal products usually involves biological analytical techniques which have a greater variability than physico-chemical determinations. In-process controls therefore acquire a great importance in the manufacture of biological medicinal products.

Personnel

1. All personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where biological medicinal products are manufactured must receive additional training specific to the products manufactured and to their work. Personnel must be given relevant information and training in hygiene and microbiology.

2. Persons responsible for production and quality control must have an adequate background in relevant scientific disciplines, such as bacteriology, biology, biometry, chemistry, medicine, pharmacy, pharmacology, virology, immunology and veterinary medicine, together with sufficient practical experience to enable them to exercise their management function for the process concerned.

3. The immunological status of personnel may have to be taken into consideration for product safety. All personnel engaged in production, maintenance, testing and animal care (and inspectors) must be vaccinated where necessary with appropriate specific vaccines and have regular health checks. Apart from the obvious problem of exposure of staff to infectious agents, potent toxins or allergens, it is necessary to avoid the risk of contamination of a production batch with infectious agents. Visitors must generally be excluded from production areas.

4. Any changes in the immunological status of personnel which could adversely affect the quality of the product must preclude work in the production area. Production of BCG vaccine and tuberculin products must be restricted to staff who are carefully monitored by regular checks of immunological status or chest X-ray.

5. In the course of a working day, personnel must not pass from areas where exposure to live organisms or animals is possible to areas where other products or different organisms are handled. If such passage is unavoidable, clearly defined decontamination measures, including change of clothing and shoes and, where necessary, showering must be followed by staff involved in any such production.

Premises and equipment

6. The degree of environmental control of particulate and microbial contamination of the production premises must be adapted to the product and the production stages, bearing in mind the level of contamination of the starting materials and the risk to the finished product.

7. The risk of cross-contamination between biological medicinal products, especially during those stages of the manufacturing process in which live organisms are used, may require additional precautions with respect to facilities and equipment, such as the use of dedicated facilities and equipment, production on a campaign basis and the use of closed systems. The nature of the product as well as the equipment used will determine the level of segregation needed to avoid cross-contamination.

8. In principle, dedicated facilities must be used for the production of BCG vaccine and for the handling of live organisms used in production of tuberculin products.

9. Dedicated facilities must be used for the handling of *Bacillus anthracis*, of *Clostridium*

botulinum and of *Clostridium tetani* until the inactivation process is accomplished.

10. Production on a campaign basis may be acceptable for other spore forming organisms provided that the facilities are dedicated to this group of products and not more than one product is processed at any one time.
11. Simultaneous production in the same area using closed systems of bio fermenters may be acceptable for products such as monoclonal antibodies and products prepared by DNA techniques.
12. Processing steps after harvesting may be carried out simultaneously in the same production area provided that adequate precautions are taken to prevent cross contamination. For killed vaccines and toxoids, such parallel processing must only be performed after inactivation of the culture or after detoxification.
13. Positive pressure areas must be used to process sterile products but negative pressure in specific areas at point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or safety cabinets are used for aseptic processing of pathogens, they must be surrounded by a positive pressure sterile zone.
14. Air filtration units must be specific to the processing area concerned and recirculation of air must not occur from areas handling live pathogenic organisms.
15. The layout and design of production areas and equipment must permit effective cleaning and decontamination (e.g. by fumigation). The adequacy of cleaning and decontamination procedures must be validated.
16. Equipment used during handling of live organisms must be designed to maintain cultures in a pure state and uncontaminated by external sources during processing.
17. Pipework systems, valves and vent filters must be properly designed to facilitate cleaning and sterilisation. The use of 'clean in place' and 'sterilise in place' systems must be encouraged. Valves on fermentation vessels must be completely steam sterilisable. Air vent filters must be hydrophobic and validated for their scheduled life span.
18. Primary containment must be designed and tested to demonstrate freedom from leakage risk.
19. Effluents which may contain pathogenic micro-organisms must be effectively decontaminated.
20. Due to the variability of biological products or processes, some additives or ingredients must be measured or weighed during the production process (e.g. buffers). In these cases, small stocks of these substances may be kept in the production area.

Animal quarters and care

21. Animals are used for the manufacture of a number of biological products, for example polio vaccine (monkeys), snake antivenoms (horses and goats), rabies vaccine (rabbits, mice and hamsters) and serum gonadotropin (horses). Moreover, animals may also be used in the quality control of most sera and vaccines, e.g. pertussis vaccine (mice), pyrogenicity (rabbits), BCG vaccine (guinea-pigs).
22. General requirements for animal quarters, care and quarantine are laid down in Law No. 471/2002 (The Official Gazette of Romania, No. 535 of 23 July 2002) on approval of Government Ordinance No. 37/2002 on the protection of animals used for scientific or other experimental purposes (The Official Gazette of Romania, No. 95 of 2 February 2002). Quarters for animals used in production and control of biological products must be separated from production and control areas. The health status of animals from which some starting materials are derived and of those used for quality control and safety testing must be monitored and recorded. Staff employed in such areas must be provided with special

clothing and changing facilities. Where monkeys are used for the production or quality control of biological medicinal products, special consideration is required as laid down in the current WHO Requirements for Biological Substances No. 7.

Documentation

23. Specifications for biological starting materials may need additional documentation related to the source, origin, method of manufacture and controls applied, particularly microbiological controls.

24. Specifications are routinely required for intermediate and bulk biological medicinal products.

Production

Starting materials

25. The source, origin and suitability of starting materials must be clearly defined. Where the necessary tests take a long time, it may be permissible to process starting materials before the results of the tests are available. In such cases, release of a finished product is conditioned by satisfactory results of these tests.

26. Where sterilisation of starting materials is required, it must be carried out where possible by heat. Where necessary, other appropriate methods may also be used for inactivation of biological materials (e.g. irradiation).

Seed lot and cell bank system

27. In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of biological medicinal products obtained by microbial culture, cell culture or propagation in embryos and animals must be based on a system of master and working seed lots and/or cell banks.

28. The number of generations (doublings, passages) between the seed lot or cell bank and the finished product must be compliant with the marketing authorisation dossier. Scaling up of the process must not change this fundamental relationship.

29. Seed lots and cell banks must be adequately characterised and tested for contaminants. Their suitability for use must be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Seed lots and cell banks must be established, stored and used in such a way as to minimise the risks of contamination or alteration.

30. Establishment of the seed lot and cell bank must be performed in a suitably controlled environment to protect the seed lot and the cell bank and, if applicable, the personnel handling it. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) must be handled simultaneously in the same area or by the same persons.

31. Evidence of the stability and recovery of the seeds and banks must be documented. Storage containers must be hermetically sealed, clearly labelled and kept at an appropriate temperature. An inventory must be meticulously kept. Storage temperature must be recorded continuously for freezers and properly monitored for liquid nitrogen. Any deviation from set limits and any corrective action taken must be recorded.

32. Only authorised personnel must be allowed to handle the material and this handling must be done under the supervision of a responsible person. Access to stored material must be controlled. Different seed lots or cell banks must be stored in such a way to avoid confusion or cross-contamination. It is desirable to split the seed lots and cell banks and to store the parts at different locations so as to minimise the risks of total loss.

33. All containers of master or working cell banks and seed lots must be treated identically during storage. Once removed from storage, the containers must not be returned to the stock.

Operating principles

34. The growth promoting properties of culture media must be demonstrated.

35. Addition of materials or cultures to fermenters and other vessels and the taking of samples must be carried out under carefully controlled conditions to ensure that absence of contamination is maintained. Care must be taken to ensure that vessels are correctly connecting when addition or sampling take place.

36. Centrifugation and blending of products can lead to aerosol formation, and containment of such activities to prevent transfer of live microorganisms is necessary.

37. If possible, media must be sterilised "*in situ"*. In-line sterilising filters for routine addition of gases, media, acids or alkalis, defoaming agents etc. to fermenters must be used where possible.

38. Careful consideration must be given to the validation of any necessary virus removal or inactivation undertaken (see the guidelines issued by the Committee for Proprietary Medicinal Products).

39. In cases where a virus inactivation or removal process is performed during manufacture, measures must be taken to avoid the risk of recontamination of treated products by non-treated products.

40. A wide variety of equipment is used for chromatography, and in general such equipment must be dedicated to the purification of one product and must be sterilised or sanitised between batches. The use of the same equipment at different stages of processing must be discouraged. Acceptance criteria, life span and sanitation or sterilisation method of columns must be defined.

Quality control

41. In-process controls play a particularly important role in ensuring the consistency of the quality of biological medicinal products. Those controls which are crucial for quality (e.g. virus removal) but which cannot be carried out on the finished product must be performed at an appropriate stage of production.

42. It may be necessary to retain samples of intermediate products in sufficient quantities and under appropriate storage conditions to allow the repetition or confirmation of a batch control.

43. Continuous monitoring of certain production processes is necessary (e.g. fermentation). Such data must form part of the batch record.

44. Where continuous culture is used, special consideration must be given to the quality control requirements arising from this type of production method.

ANNEX 3

MANUFACTURE OF RADIOPHARMACEUTICALS

Principle

The manufacture of radiopharmaceuticals shall be undertaken in accordance with the principles of Good Manufacturing Practice for Medicinal Products Part I and II. This annex specifically addresses some of the practices, which may be specific for radiopharmaceuticals.

Note i. Preparation of radiopharmaceuticals in radiopharmacies (hospitals or certain pharmacies), using Generators and Kits with a marketing authorisation or a national licence, is not covered by this guideline, unless covered by national requirement.

Note ii. According to radiation protection regulations it must be ensured that any medical exposure is under the clinical responsibility of a practitioner. In diagnostic and therapeutic nuclear medicine practices a medical physics expert shall be available.

Note iii. This annex is also applicable to radiopharmaceuticals used in clinical trials.

Note iv. Transport of radiopharmaceuticals is regulated by the International Atomic Energy Association (IAEA) and radiation protection requirements.

Note v. It is recognised that there are acceptable methods, other than those described in this annex, which are capable of achieving the principles of Quality Assurance. Other methods must be validated and provide a level of Quality Assurance at least equivalent to those set out in this annex.

Introduction

1. The manufacturing and handling of radiopharmaceuticals is potentially hazardous. The level of risk depends in particular upon the types of radiation, the energy of radiation and the half-lives of the radioactive isotopes. Particular attention must be paid to the prevention of cross contamination, to the retention of radionuclide contaminants, and to waste disposal.

2. Due to short shelf-life of their radionuclides, some radiopharmaceuticals may be released before completion of all quality control tests. In this case, the exact and detailed description of the whole release procedure including the responsibilities of the involved personnel and the continuous assessment of the effectiveness of the quality assurance system is essential.

3. This guideline is applicable to manufacturing procedures employed by industrial manufacturers, Nuclear Centres/Institutes and PET Centres for the production and quality control of the following types of products:

   - Radiopharmaceuticals
   - Positron Emitting (PET) Radiopharmaceuticals
   - Radioactive Precursors for radiopharmaceutical production
   - Radionuclide Generators

Type of manufacture	***Non-GMP****	***GMP part II & I including relevant annexes***			
Radiopharmaceuticals PET Radiopharmaceuticals Radioactive Precursors	*Reactor/ Cyclotron production*	*Chemical synthesis*	*Purification steps*	*Procession, formulation and dispensing*	*Aseptic or final sterilisation*
Radionuclide Generators	*Reactor/ Cyclotron production*	*Processing*			

** Target and transfer system from cyclotron to synthesis rig may be considered as the first step of active substance manufacture.*

4. The manufacturer of the final radiopharmaceutical must describe and justify the steps for manufacture of the active substance and the final medicinal product and which GMP (part I or II) applies for the specific process/manufacturing steps.
5. Preparation of radiopharmaceuticals involves adherence to regulations on radiation protection.
6. Radiopharmaceuticals to be administered parenterally must comply with sterility requirements for parenterals and, where relevant, aseptic working conditions for the manufacture of sterile medicinal products, which are covered in the Guideline on Good Manufacturing Practice, Annex 1.
7. Specifications and quality control testing procedures for the most commonly used radiopharmaceuticals are specified in the European Pharmacopoeia or in the marketing authorisation.

Clinical Trials

8. Radiopharmaceuticals intended for use in clinical trials as investigational medicinal products must in addition be manufactured in accordance with the principles stated in the Guideline for Good Manufacturing Practice, Annex 13.

Quality assurance

9. Quality assurance is of even greater importance in the manufacture of radiopharmaceuticals because of their particular characteristics, low volumes and in some circumstances the need to administer the product before testing is complete.
10. As with all pharmaceuticals, the products must be well protected against contamination and cross-contamination. However, the environment and the operators must also be protected against radiation. This means that the role of an effective quality assurance system is of the utmost importance.
11. It is important that the data generated by the monitoring of premises and processes are rigorously recorded and evaluated as part of the release process.
12. The principles of qualification and validation must be applied to the manufacturing of radiopharmaceuticals and a risk management approach must be used to determine the degree of qualification/validation, focusing on a combination of Good Manufacturing Practice and Radiation Protection.

Personnel

13. All manufacturing operations must be carried out under the responsibility of personnel with additional competence in radiation protection. Personnel involved in production, analytical control and release of radio-pharmaceuticals must be properly trained in radiopharmaceutical specific aspects of the quality management system. The QP must have the overall responsibility for release of the products.
14. All personnel (including those concerned with cleaning and maintenance) employed in areas where radioactive products are manufactured must receive appropriate additional training specific to these types of products.

15. Where production facilities are shared with research institutions, the research personnel must be adequately trained in GMP regulations and the QA function must review and approve the research activities to ensure that they do not pose any hazard to the manufacturing of radiopharmaceuticals.

Premises and equipment

General

16. Radioactive products must be manufactured in controlled (environmental and radioactive) areas. All manufacturing steps must take place in self-contained facilities dedicated to radiopharmaceuticals.
17. Measures must be established and implemented to prevent cross-contamination from personnel, materials, radionuclides etc. Closed or contained equipment must be used whenever appropriate. Where open equipment is used, or equipment is opened, precautions must be taken to minimize the risk of contamination. The risk assessment must demonstrate that the proposed environmental cleanliness level is suitable for the type of product being manufactured.
18. Access to the manufacturing areas must be via a gowning area and must be restricted to authorised personnel.
19. Workstations and their environment must be monitored with respect to radioactivity, particulate and microbiological quality as established during performance qualification (PQ).
20. Preventive maintenance, calibration and qualification programmes must be operated to ensure that all facilities and equipment used in the manufacture of radiopharmaceutical are suitable and qualified. These activities must be carried out by competent personnel and records and logs must be maintained.
21. Precautions must be taken to avoid radioactive contamination within the facility. Appropriate controls must be in place to detect any radioactive contamination, either directly through the use of radiation detectors or indirectly through a swabbing routine.
22. Equipment must be constructed so that surfaces that come into contact with the product are not reactive, additive or absorptive so as to alter the quality of the radiopharmaceutical.
23. Re-circulation of air extracted from area where radioactive products are handled must be avoided unless justified. Air outlets must be designed to minimize environmental contamination by radioactive particles and gases and appropriate measures must be taken to protect the controlled areas from particulate and microbial contamination.
24. In order to contain radioactive particles, it may be necessary for the air pressure to be lower where products are exposed, compared with the surrounding areas. However, it is still necessary to protect the product from environmental contamination. This may be achieved by, for example, using barrier technology or airlocks, acting as pressure sinks.

Sterile production

25. Sterile radiopharmaceuticals may be divided into those, which are manufactured aseptically, and those, which are terminally sterilised. The facility must maintain the appropriate level of environmental cleanliness for the type of operation being performed. For manufacture of sterile products the working zone where products or containers may be exposed to the environment, the cleanliness requirements must comply with the requirements described in the Annex referring to sterile medicinal products.
26. For manufacture of radiopharmaceuticals a risk assessment may be applied to determine the appropriate pressure differences, air flow direction and air quality.
27. In case of use of automated closed systems (chemical synthesis, purification, sterile filtration) a grade C environment (usually “Hot-cell”) will be suitable. Hot-cells must meet a high degree of air cleanliness, with filtered feed air, when closed. Aseptic activities must be carried out in a grade A area.

28. Prior to the start of manufacturing, assembly of sterilised equipment and consumables (tubing, sterilised filters and sterile closed and sealed vials to a sealed fluid path) must be performed under aseptic conditions.

Documentation

29. All documents related to the manufacture of radiopharmaceuticals must be prepared, reviewed, approved and distributed in accordance with written procedures.
30. Specifications must be established and documented for raw materials, labelling and packaging materials, critical intermediates and the finished radiopharmaceutical. Specifications must also be in place for any other critical items used in the manufacturing process, such as process aids, gaskets, sterile filtering kits, that could have a critical impact upon quality.
31. Acceptance criteria must be established for the radiopharmaceutical including criteria for release and shelf life specifications (examples: chemical identity of the isotope, radioactive concentration, purity, and specific activity).
32. Records of major equipment use, cleaning, sanitisation or sterilisation and maintenance must show the product name and batch number, where appropriate, in addition to the date and time and signature for the persons involved in these activities.
33. Records must be retained for at least 3 years unless another timeframe is specified in national requirements.

Production

34. Production of different radioactive products in the same working area (i.e. hot-cell, LAF unit), at the same time must be avoided in order to minimise the risk of radioactive cross-contamination or mix-up.
35. Special attention must be paid to validation including validation of computerised systems which must be carried out in accordance in compliance with Annex 11. New manufacturing processes must be validated prospectively.
36. The critical parameters must normally be identified before or during validation and the ranges necessary for reproducible operation must be defined.
37. Integrity testing of the membrane filter must be performed for aseptically filled products, taking into account the need for radiation protection and maintenance of filter sterility.
38. Due to radiation exposure it is accepted that most of the labelling of the direct container, is done prior to manufacturing. Sterile empty closed vials may be labeled with partial information prior to filling providing that this procedure does not compromise sterility or prevent visual control of the filled vial.

Quality control

39. Some radiopharmaceuticals may have to be distributed and used on the basis of an assessment of batch documentation and before all chemical and microbiology tests have been completed. Radiopharmaceutical product release may be carried out in two or more stages, before and after full analytical testing:

a) Assessment by a designated person of batch processing records, which must cover production conditions and analytical testing performed thus far, before allowing transportation of the radiopharmaceutical under quarantine status to the clinical department.

b) Assessment of the final analytical data, ensuring all deviations from normal procedures are documented, justified and appropriately released prior to documented certification by the Qualified Person (QP).

Where certain test results are not available before the product's use, the Qualified Person must conditionally certify the product before it is used and must finally certify the product after all the test results are obtained.

40. Most radiopharmaceuticals are intended for use within a short time and the period of validity with regard to the radioactive shelf-life, must be clearly stated.
41. Radiopharmaceuticals having radionuclides with long half-lives must be tested to show that they meet all relevant acceptance criteria before release and certification by the QP.
42. Before testing is performed samples can be stored to allow sufficient radioactivity decay. All tests including the sterility test must be performed as soon as possible.
43. A written procedure detailing the assessment of production and analytical data, which must be considered before the batch is dispatched, must be established.
44 Products that fail to meet acceptance criteria must be rejected. If the material is reprocessed, pre-established procedures must be followed and the finished product must meet acceptance criteria before release. Returned products may not be reprocessed and must be stored as radioactive waste.
45. A procedure must also describe the measures to be taken by the Qualified Person if unsatisfactory test results (Out-of-Specification) are obtained after dispatch and before expiry. Such events must be investigated to include the relevant corrective and preventative actions taken to prevent future events. This process must be documented.
46. Information must be given to the clinical responsible persons, if necessary. To facilitate this, a traceability system must be implemented for radiopharmaceuticals.
47. A system to verify the quality of starting materials must be in place. Supplier approval must include an evaluation that provides adequate assurance that the material consistently meets specifications. The starting materials, packaging materials and critical process aids must be purchased from approved suppliers.

Reference and retention samples

48. For radiopharmaceuticals sufficient samples of each batch of bulk formulated product shall be retained for at least six months after expiry of the finished medicinal product unless otherwise justified through risk management.
49. Samples of starting materials, other than solvents gases or water used in the manufacturing process shall be retained for at least two years after the release of the product. That period may be shortened if the period of stability of the material as indicated in the relevant specification is shorter.
50. Other conditions may be defined by agreement with the competent authority, for the sampling and retaining of starting materials and products manufactured individually or in small quantities or when their storage could raise special problems.

Distribution

51. Distribution of the finished product under controlled conditions, before all appropriate test results are available, is acceptable for radiopharmaceuticals, providing the product is not administered by the receiving institute until satisfactory test results has been received and assessed by a designated person.

Glossary

Hot–cells: shielded workstations for manufacture and handling of radioactive materials. Hot-cells are not necessarily designed as an isolator.

Manufacturing: production, quality control and release and delivery of radiopharmaceuticals from the active substance and starting materials.

Preparation: handling and radiolabelling of kits with radionuclide eluted from generators or radioactive precursors within a hospital. Kits, generators and precursors must have a marketing authorization.

Qualified person: QP as described in Law No. 95/2006. QP responsibilities are stated in Annex 16.

ANNEX 4

MANUFACTURE OF VETERINARY MEDICINAL PRODUCTS, OTHER THAN IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS*

ANNEX 5

MANUFACTURE OF IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS *

ANNEX 6

MANUFACTURE OF MEDICINAL GASES

Principle

Gases which fulfil the definition of medicinal product of Law No. 95/2006, Title XVII – The medicinal product (hereinafter, medicinal gases) are subject to the requirements laid down in this Law, including the requirements on manufacturing. In this regard, this Annex deals with the manufacture of active substance gases and with the manufacture of medicinal gases.

The delineation between the manufacture of the active substance and the manufacture of the medicinal product must be clearly defined in each Marketing Authorisation dossier. Normally, the production and purification steps of the gas belong to the field of manufacture of active substances. Gases enter the pharmaceutical field from the first storage of gas intended for such use.

Manufacture of active substance gases must comply with the Basic Requirements of this Guideline (Part II), with the relevant part of this Annex, and with the other Annexes of the guide if relevant.

Manufacture of medicinal gases must comply with the Basic Requirements of this Guideline (Part I), with the relevant part of this Annex, and with the other Annexes of the guide if relevant.

In the exceptional cases of continuous processes where no intermediate storage of gas between the manufacture of the active substance and the manufacture of the medicinal product is possible, the whole process (from starting materials of active substance to medicinal finished product) must be considered as belonging to the pharmaceutical field. This must be clearly stated in the Marketing Authorisation dossier.

The Annex does not cover the manufacture and handling of medicinal gases in hospitals unless this is considered industrial preparation or manufacturing. However, relevant parts of this Annex may be used as a basis for such activities.

Manufacture of active substance gases

Active substance gases can be prepared by chemical synthesis or be obtained from natural sources followed by purification steps, if necessary (for example in an air separation plant).

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* Not adopted as part of this Guideline

1. The processes corresponding to these two methods of manufacturing active substance gases must comply with Part II of the Basic Requirements. However:

(a) the requirements regarding starting materials for active substances (Part II Chapter 7) do not apply to the production of active substance gases by air separation (however, the manufacturer must ensure that the quality of ambient air is suitable for the established process and any changes in the quality of ambient air do not affect the quality of the active substance gas);

(b) the requirements regarding ongoing stability studies (Part II chapter 11.5), which are used to confirm storage conditions and expiry/retest dates (Part II chapter 11.6), do not apply in case initial stability studies have been replaced by bibliographic data (see Note for Guidance CPMP/QWP/1719/00); and

(c) the requirements regarding reserve/retention samples (Part II chapter 11.7) do not apply to active substance gases, unless otherwise specified.

2. The production of active substance gases through a continuous process (e.g. air separation) must be continuously monitored for quality. The results of this monitoring must be kept in a manner permitting trend evaluation.

3. In addition:

(a) transfers and deliveries of active substance gases in bulk must comply with the same requirements as those mentioned below for medicinal gases (sections 19 to 21 of this Annex);

(b) filling of active substance gases into cylinders or into mobile cryogenic vessels must comply with the same requirements as those mentioned below for the medicinal gases (sections 22 to 37 of this Annex) as well as Part II Chapter 9.

Manufacture of medicinal gases

The manufacture of medicinal gases is generally carried out in closed equipment. Consequently, environmental contamination of the product is minimal. However, risks of contamination (or cross contamination with other gases) may arise, in particular because of the reuse of containers.

4. Requirements applying to cylinders must also apply to cylinders bundles (except storage and transportation under cover).

Personnel

5. The entire personnel involved in manufacture and distribution of medicinal gases must receive an appropriate GMP training specifically applying to this type of products.

They must be aware of the critically important aspects and potential hazards for patients from these products. The training programs must include the tanker lorry drivers.

6. Personnel of subcontractors that could influence the quality of medicinal gases (such as personnel in charge of maintenance of cylinders or valves) must be appropriately trained.

Premises and equipment

Premises

7. Cylinders and mobile cryogenic vessels must be checked, prepared, filled and stored in separate areas from non-medicinal gases, and there must be no exchange of cylinders/mobile cryogenic vessels between these areas. However, it could be accepted to check, prepare, fill and store other gases in the same areas, provided they comply with the specifications of medicinal gases and that the manufacturing operations are performed according to GMP standards.

8. Premises must provide sufficient space for manufacturing, testing and storage operations in order to prevent any risk of mix-up. Premises must be designed to provide:

a. separate marked areas for different gases;

b. clear identification and segregation of cylinders/mobile cryogenic vessels at various stages of processing (e.g. “waiting checking” "awaiting filling", "quarantine", "certified", “rejected” “prepared deliveries”).

The method used to achieve these various levels of segregation will depend on the nature, extent and complexity of the overall operation. Marked-out floor areas, partitions, barriers, signs, labels or other appropriate means could be used.

9. Empty cylinders/home cryogenic vessels after sorting or maintenance, and filled cylinders/home cryogenic vessels must be stored under cover, protected from adverse weather conditions. Filled cylinders/mobile cryogenic vessels must be stored in a manner that ensures that they will be delivered in a clean state, compatible with the environment in which they will be used.

10. Specific storage conditions must be provided as required by the Marketing Authorisation (e.g. for gas mixtures where phase separation occurs in case of freezing).

Equipment

11. Equipment must be designed to ensure the correct gas is filled into the correct container. There must normally be no cross connections between pipelines carrying different gases. If cross connections are needed (e.g. filling equipment of mixtures), qualification must ensure that there is no risk of cross contamination between the different gases. In addition, the manifolds must be equipped with specific connections. These connections may be subject to national or international standards. The use of connections meeting different standards at the same filling site must be carefully controlled, as well as the use of adaptors needed in some situations to bypass the specific fill connection systems.

12. Tanks and tankers must be dedicated to a single and defined quality of gas. However medicinal gases may be stored or transported in the same tanks, other containers used for intermediate storage, or tankers, as the same non-medicinal gas, provided that the quality of the latter is at least equal to the quality of the medicinal gas and that GMP standards are maintained. In such cases, quality risk management must be performed and documented.

13. A common system supplying gas to medicinal and non-medicinal gas manifolds is only acceptable if there is a validated method to prevent backflow from the non-medicinal gas line to the medicinal gas line.

14. Filling manifolds must be dedicated to a single medicinal gas or to a given mixture of medicinal gases. In exceptional cases, filling gases used for other medical purposes on manifolds dedicated to medicinal gases may be acceptable if justified and performed under control. In these cases, the quality of the non-medicinal gas must be at least equal to the required quality of the medicinal gas and GMP standards must be maintained. Filling must then be carried out by campaigns.

15. Repair and maintenance operations (including cleaning and purging) of equipment, must not adversely affect the quality of medicinal gases. In particular, procedures must describe the measures to be taken after repair and maintenance operations involving breaches of the system’s integrity. Specifically it must be demonstrated that the equipment is free from any contamination that may adversely affect the quality of the finished product before releasing it for use. Records must be maintained.

16. A procedure must describe the measures to be taken when a tanker is back into medicinal gas service (after transporting non-medicinal gas in the conditions mentioned in section 12 or after a maintenance operation). This must include analytical testing.

4. Documentation

17. Data included in the records for each batch of cylinders/mobile cryogenic vessels must ensure that each filled container is traceable to significant aspects of the relevant filling operations. As appropriate, the following must be entered:

(a) name of the product;

(b) batch number;

(c) date and time of the filling operation;
(d) identification of the person(s) carrying out each significant step (e.g. line clearance, receipt, preparation before filling, filling etc.);
(e) batch(es) reference(s) for the gas(es) used for the filling operation as referred to in section 22, including status;
(f) equipment used (e.g. filling manifold);
(g) quantity of cylinders/mobile cryogenic vessels before filling, including individual identification references and water capacity(ies);
(h) pre-filling operations performed (see section 30);
(i) key parameters that are needed to ensure correct filling at standard conditions;
(j) results of appropriate checks to ensure the cylinders/mobile cryogenic vessels have been filled;
(k) a sample of the batch label;
(l) specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment);
(m) quantity of rejected cylinders/mobile cryogenic vessels, with individual identification references and reasons for rejections;
(n) details of any problems or unusual events, and signed authorisation for any deviation from filling instructions; and
(o) certification statement by the Qualified Person, date and signature.

18. Records must be maintained for each batch of gas intended to be delivered into hospital tanks. These records must, as appropriate, include the following (items to be recorded may vary depending on local legislation):
(a) name of the product;
(b) batch number;
(c) identification reference for the tank (tanker) in which the batch is certified;
(d) date and time of the filling operation;
(e) identification of the person(s) carrying out the filling of the tank (tanker);
(f) reference to the supplying tanker (tank), reference to the source gas as applicable;
(g) relevant details concerning the filling operation;
(h) specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment);
(i) details of any problems or unusual events and signed authorisation for any deviation from filling instructions; and
(j) certification statement by the Qualified Person, date and signature.

Production

Transfers and deliveries of cryogenic and liquefied gas

19. The transfers of cryogenic or liquefied gases from primary storage, including controls before transfers, must be in accordance with validated procedures designed to avoid the possibility of contamination. Transfer lines must be equipped with non-return valves or other suitable alternatives. Flexible connections, coupling hoses and connectors must be flushed with the relevant gas before use.
20. The transfer hoses used to fill tanks and tankers must be equipped with product-specific connections. The use of adaptors allowing the connection of tanks and tankers not dedicated to the same gases must be adequately controlled.
21. Deliveries of gas may be added to tanks containing the same defined quality of gas provided that a sample is tested to ensure that the quality of the delivered gas is acceptable. This sample may be taken from the gas to be delivered or from the receiving tank after delivery.

Note: See specific arrangements in section 42 for filling of tanks retained by customers at the customer's premises.

Filling and labelling of cylinders and mobile cryogenic vessels

22. Before filling cylinders and mobile cryogenic vessels, a batch (batches) of gas(es) must be determined, controlled according to specifications and approved for filling.
23. In the case of continuous processes as those mentioned in 'Principle', there must be adequate in-process controls to ensure that the gas complies with specifications.
24. Cylinders, mobile cryogenic vessels and valves must be compliant with appropriate technical specifications and any relevant requirements of the Marketing Authorisation. They must be dedicated to a single medicinal gas or to a given mixture of medicinal gases. Cylinders must be colour-coded according to relevant standards. They must preferably be fitted with minimum pressure retention valves with non-return mechanism in order to provide adequate protection against contamination.
25. Cylinders, mobile cryogenic vessels and valves must be checked before first use in production, and must be properly maintained. Where CE marked medical devices are used, the maintenance must address the medical device manufacturer's instructions.
26. Checks and maintenance operations must not affect the quality and the safety of the medicinal product. The water used for the hydrostatic pressure testing carried out on cylinders must be at least of drinking quality.
27. As part of the checks and maintenance operations, cylinders must be subject to an internal visual inspection before fitting the valve, to make sure they are not contaminated with water or other contaminants. This must be done:
    - when they are new and initially put into medicinal gas service;
    - following any hydrostatic statutory pressure test or equivalent test where the valve is removed;
    - whenever the valve is replaced.

    After fitting, the valve must be kept closed to prevent any contamination from entering the cylinder. If there is any doubt about the internal condition of the cylinder, the valve must be removed and the cylinder internally inspected to ensure it has not been contaminated.
28. Maintenance and repair operations of cylinders, mobile cryogenic vessels and valves are the responsibility of the manufacturer of the medicinal product. If subcontracted, they must only be carried out by approved subcontractors, and contracts including technical agreements must be established. Subcontractors must be audited to ensure that appropriate standards are maintained.
29. There must be a system to ensure the traceability of cylinders, mobile cryogenic vessels and valves.
30. Checks to be performed before filling must include:

    (a) In the case of cylinders, a check, carried out according to defined procedure, to ensure there is a positive residual pressure in each cylinder;

    - if the cylinder is fitted with a minimum pressure retention valve, when there is no signal indicating there is a positive residual pressure, the correct functioning of the valve must be checked, and if the valve is shown not to function properly the cylinder must be sent to maintenance;
    - if the cylinder is not fitted with a minimum pressure retention valve, when there is no positive residual pressure the cylinder must be put aside for additional measures, to make sure it is not contaminated with water or other contaminants; additional

measures could consist of internal visual inspection followed by cleaning using a validated method;

(b) a check to ensure that all previous batch labels have been removed;

(c) a check that any damaged product labels have been removed and replaced;

(d) a visual external inspection of each cylinder, mobile cryogenic vessel and valve for dents, arc burns, debris, other damage and contamination with oil or grease; cleaning must be done if necessary;

(e) a check of each cylinder or mobile cryogenic vessel outlet connection to determine that it is the proper type for the particular gas involved;

(f) a check of the date of the next test to be performed on the valve (in the case of valves that need to be periodically tested);

(g) a check of the cylinders or mobile cryogenic vessels to ensure that any tests required by national or international regulations (e.g. hydrostatic pressure test or equivalent for cylinders) have been conducted and are still valid; and

(h) A check to determine that each cylinder is colour-coded as specified in the Marketing Authorisation (colour-coding of the relevant national / international standards).

31. A batch must be defined for filling operations.

32. Cylinders that have been returned for refilling must be prepared with care in order to minimise the risks of contamination, in line with the procedures defined in the Marketing Authorisation.

These procedures, which must include evacuation and/or purging operations, must be validated.

Note: For compressed gases, a maximum theoretical impurity of 500 ppm v/v must be obtained for a filling pressure of 200 bar at 15°C (and equivalent for other filling pressures).

33. Mobile cryogenic vessels that have been returned for refilling must be prepared with care in order to minimise the risks of contamination, in line with the procedures defined in the Marketing Authorisation. In particular, mobile vessels with no residual pressure must be prepared using a validated method.

34. There must be appropriate checks to ensure that each cylinder/mobile cryogenic vessel has been properly filled.

35. Each filled cylinder must be tested for leaks using an appropriate method, prior to fitting the tamper evident seal (see section 36). The test method must not introduce any contaminant into the valve outlet and, if applicable, must be performed after any quality sample is taken.

36. After filling, cylinder valves must be covered to protect the outlets from contamination. Cylinders and mobile cryogenic vessels must be fitted with tamper-evident seals.

37. Each cylinder or mobile cryogenic vessel must be labelled. The batch number and the expiry date may be on a separate label.

38. In the case of medicinal gases produced by mixing two or more different gases (in-line before filling or directly into the cylinders); the mixing process must be validated to ensure that the gases are properly mixed in every cylinder and that the mixture is homogeneous.

Quality Control

39. Each batch of medicinal gas (cylinders, mobile cryogenic vessels, hospital tanks) must be tested in accordance with the requirements of the Marketing Authorisation and certified.

40. Unless different provisions are required in the Marketing Authorisation, the sampling plan and the analysis to be performed must comply, in the case of cylinders with the following requirements:

(a) In the case of a single medicinal gas filled into cylinders via a multi-cylinder manifold, the gas from at least one cylinder from each manifold filling cycle must be tested for identity and assay each time the cylinders are changed on the manifold.

(b) In the case of a single medicinal gas filled into cylinders one at a time, the gas from at least one cylinder of each uninterrupted filling cycle must be tested for identity and assay. An example of an uninterrupted filling cycle is one shift's production using the same personnel, equipment, and batch of gas to be filled.

(c) In the case of a medicinal gas produced by mixing two or more gases in a cylinder from the same manifold, the gas from every cylinder must be tested for assay and identity of each component gas. For excipients, if any, testing on identity could be performed on one cylinder per manifold filling cycle (or per uninterrupted filling cycle in case of cylinders filled one at a time). Fewer cylinders may be tested in case of validated automated filling system.

(d) Premixed gases must follow the same principles as single gases when continuous in-line testing of the mixture to be filled is performed.

Premixed gases must follow the same principle as medicinal gases produced by mixing gases in the cylinders when there is no continuous in-line testing of the mixture to be filled.

Testing for water content must be performed unless otherwise justified.

Other sampling and testing procedures that provide at least equivalent level of quality assurance may be justified.

41. Unless different provisions are required in the Marketing Authorisation, final testing on mobile cryogenic vessels must include a test for assay and identity on each vessel. Testing by batches must only be carried out if it has been demonstrated that the critical attributes of the gas remaining in each vessel before refilling have been maintained.
42. Cryogenic vessels retained by customers (hospital tanks or home cryogenic vessels), which are refilled in place from dedicated tankers do not need to be sampled after filling provided that a certificate of analysis on the contents of the tanker accompanies the delivery. However, it must be demonstrated that the specification of the gas in the vessels is maintained over the successive refilling.
43. Reference and retention samples are not required, unless otherwise specified.
44. On-going stability studies are not required in case initial stability studies have been replaced by bibliographic data (see Note for Guidance CPMP/QWP/1719/00).

Transportation of packaged gases

45. Filled gas cylinders and home cryogenic vessels must be protected during transportation, so that, in particular, they are delivered to customers in a clean state compatible with the environment in which they will be used.

Glossary

Active substance gas

Any gas intended to be an active substance for a medicinal product.

Air separation

Separation of atmospheric air into its constituent gases using fractional distillation at cryogenic temperatures.

Compressed gas

Gas which, when packaged under pressure for transport, is entirely gaseous at all temperatures above –50°C.

Container

A container is a cryogenic vessel (tank, tanker or other type of mobile cryogenic vessel) a cylinder, a cylinder bundle or any other package that is in direct contact with the gas.

Cryogenic gas

A gas which liquefies at 1013 bar at temperatures below –150°C.

Cylinder

Container usually cylindrical suited for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature.

Cylinder bundle

An assembly of cylinders that are fastened together, interconnected by a manifold and transported and used as a unit.

Evacuate

To remove the residual gas from a container / system to a pressure less than 1.013 bar, using a vacuum system.

Gas

Any substance that is completely gaseous at 1 013 bar and +20°C or has a vapour pressure exceeding 3 bar at +50°C.

Home cryogenic vessel

Mobile cryogenic vessel designed to hold liquid oxygen and dispense gaseous oxygen at patients' home.

Hydrostatic pressure test

Test performed as required by national or international regulations, in order to ensure that pressure containers are able to withstand pressures up to the container's design pressure.

Liquefied gas

A gas which, when packaged for transport, is partially liquid (or solid) at a temperature above $-50^{O}C$.

Manifold

Equipment or apparatus designed to enable one or more gas containers to be emptied and filled at the same time.

Maximum theoretical residual impurity

Gaseous impurity from a possible backflow that remains after the cylinder pre-treatment process before filling. The calculation of the maximum theoretical residual impurity is only relevant for compressed gases and assumes that the gases behave as perfect gases.

Medicinal gas

Any gas or mixture of gases classified as a medicinal product (as defined in Law No. 95/2006, Title XVII – The medicinal product).

Minimum pressure retention valve

A cylinder valve, which maintains a positive pressure above atmospheric pressure in a gas cylinder after use, in order to prevent internal contamination of the cylinder.

Mobile cryogenic vessel

Mobile thermally insulated container designed to maintain the contents in a liquid state. In the Annex, this term does not include the tankers.

Non-return valve

Valve, which permits flow in one direction only.

Purge

To remove the residual gas from a container / system by first pressurising and then venting the gas used for purging to 1.013 bar.

Tank

Static thermally insulated container designed for the storage of liquefied or cryogenic gas. They are also called "Fixed cryogenic vessels".

Tanker

In the context of this Annex, thermally insulated container fixed on a vehicle for the transport of liquefied or cryogenic gas.

Valve

Device for opening and closing containers.

Vent

To remove the residual gas from a container/system down to 1013 bar, by opening the container/system to atmosphere.

ANNEX 7

MANUFACTURE OF HERBAL MEDICINAL PRODUCTS

Principle

Because of their often complex and variable nature, the control of starting materials, storage and processing assume particular importance in the manufacture of herbal medicinal products.

The "starting material" in the manufacture of a herbal medicinal product1 can be a medicinal plant, a herbal substance[4] or a herbal preparation[5]. The herbal substance shall be of suitable quality and supporting data must be provided to the manufacturer of the herbal preparation/herbal medicinal product. Ensuring consistent quality of the herbal substance may require more detailed information on its agricultural production. The selection of seeds, cultivation and harvesting conditions represent important aspects of the quality of the herbal substance and can influence the consistency of the finished product. Recommendations on an appropriate quality assurance system for good agricultural and collection practice are provided in the CHMP guidance document: "Guideline on Good Agricultural and Collection Practice for starting materials of herbal origin".

This Annex applies to all herbal starting materials, namely: medicinal plants, herbal substances or herbal preparations.

[4] Throughout the annex and unless otherwise specified, the term "herbal medicinal product/ preparation" includes "traditional herbal medicinal product/ preparation".

[5] The terms herbal substance and herbal preparation as defined in Directive 2004/24/EC are considered to be equivalent to the Ph. Eur. terms herbal drug and herbal drug preparation respectively.

Table illustrating the enforcement of the Good Manufacturing Practices for herbal medicinal products [6].

Activity	**Good Agricultural and Collection Practices (GACP)[7]**	**Part II of the GMP Guideline†**	**Part I of the GMP Guideline†**
Cultivation, collection and harvesting of plants, algae, fungi and lichens, and collection of exudates			
Cutting and drying of plants, algae, fungi, lichens and exudates*			
Expression from plants and distillation**			
Comminution, processing of exudates, extraction from plants, fractionation, purification, concentration or fermentation of herbal substances			
Further processing into a dosage form including packaging as a medicinal product			

†Explanatory note

The GMP classification of the herbal material is dependent upon the use made of it by the manufacturing authorisation holder. The material may be classified as an active substance, an intermediate or a finished product. It is the responsibility of the manufacturer of the medicinal product to ensure that the appropriate GMP classification is enforced.

*Manufacturers must ensure that these steps are carried out in accordance with the marketing authorisation. For those initial steps that take place in the field, as specified in the marketing authorisation, the standards of the Good Agricultural and Collection Practice for starting materials of herbal origin (GACP) is applicable. GMP is applicable to further cutting and drying steps.

**Regarding the expression from plants and distillation, if it is necessary for these activities to be an integral part of harvesting to maintain the quality of the product within the approved specifications, it is acceptable that they are performed in the field, provided that the cultivation is in compliance with GACP. These circumstances must be regarded as exceptional and justified in the relevant marketing authorization / registration documentation. For activities carried out in the field, appropriate documentation, control, and validation according to the GMP principles must be assured. Regulatory authorities may carry out GMP inspections of these activities in order to assess compliance.

Premises and equipment

Storage areas

1. Raw herbal substances must be stored in separate areas. The storage area must be equipped in such a way as to give protection against the entry of insects or other animals, especially rodents. Effective measures must be taken to prevent the spread of any such animals and microorganisms brought in with the herbal substance, to prevent fermentation or mould

[6]This table expands in detail the herbal section of Table 1 in Part II of the GMP Guideline.

[7] As published by the European Medicines Agency (EMA).

growth and to prevent cross-contamination. Different enclosed areas must be used to quarantine incoming herbal substances and for the approved herbal substances.

2. The storage area must be well aerated and the containers must be located in such a way so as to allow free circulation of air.
3. Special attention must be paid to the cleanliness and maintenance of the storage areas particularly when dust is generated.
4. Storage of herbal substances and herbal preparations may require special conditions of humidity, temperature or light protection; these requirements must be provided and monitored.

Production area

5. Specific provisions must be made during sampling, weighing, mixing and processing operations of herbal substances and herbal preparations whenever dust is generated, to facilitate cleaning and to avoid cross-contamination, as for example, dust extraction, dedicated premises, etc.

Equipment

6. The equipment, filtering materials etc. used in the manufacturing process must be compatible with the extraction solvent, in order to prevent any release or undesirable absorption of substance that could affect the given product.

Documentation

Specifications for starting materials

7. Herbal medicinal product manufacturers must ensure that they use only herbal starting materials manufactured in accordance with GMP and the Marketing Authorisation dossier. Comprehensive documentation on audits of the herbal starting material suppliers carried out by, or on behalf of the herbal medicinal product manufacturer must be made available. Audit trails for the active substance are fundamental to the quality of the starting material. The manufacturer must ensure that the suppliers of the herbal substance/preparation are in compliance with GACP.
8. To fulfil the specification requirements described in the basic requirements of the Guide (chapter 4, section 4.11.), documentation for herbal substances/preparations must include:

- the binomial scientific name of plant (genus, species, subspecies/variety and author (e.g. Linnaeus); other relevant information such as the cultivar name and the chemotype must also be provided, as appropriate;
- details of the source of the plant (country or region of origin, and where applicable, cultivation, time of harvesting, collection procedures, possible pesticides used, etc.);
- which part(s) of the plant is/are used;
- when a dried plant is used, the drying system must be specified;
- a description of the herbal substance and its macro and microscopic examination;
- suitable identification tests including, where appropriate, identification tests for known active substances or markers. Specific distinctive tests are required where an herbal substance is liable to be adulterated/substituted. A reference authentic specimen must be available for identification purposes;
- the water content for herbal substances, determined in accordance with the European Pharmacopoeia;
- assay of constituents of known therapeutic activity or, where appropriate, of markers; the methods suitable to determine possible pesticide contamination and limits accepted, in accordance with the methods specified in the European Pharmacopoeia or, in absence thereof, with an appropriate validated method, unless otherwise justified;
- tests to determine fungal and/or microbial contamination, including aflatoxins, other mycotoxins, pest-infestations and limits accepted, as appropriate;

- tests for toxic metals and for likely contaminants and adulterants, as appropriate;
- tests for foreign materials, as appropriate;
- any other additional test according to the European Pharmacopoeia general monograph on herbal substances or to the specific monograph of the herbal substance, as appropriate.
- Any treatment used to reduce fungal/microbial contamination or other infestation must be documented. Specifications and procedures must be available and must include details of process, tests and limits for residues.

Processing instructions

9. The processing instructions must describe the different operations carried out upon the herbal substance such as cleaning, drying, crushing and sifting, and include drying time and temperatures, and methods used to control cut size or particle size.
10. In particular, there must be written instructions and records, which ensure that each container of herbal substance is carefully examined to detect any adulteration/substitution or presence of foreign matter, such as metal or glass pieces, animal parts or excrement, stones, sand, etc., or rot and signs of decay.
11. The processing instructions must also describe security sieving or other methods of removing foreign materials and appropriate procedures for cleaning/selection of plant material before the storage of the approved herbal substance or before the start of manufacturing.
12. For the production of a herbal preparation, instructions must include details of solvent, time and temperature of extraction, details of any concentration stages and methods used.

Quality Control

Sampling

13. Due to the fact that medicinal plant/herbal substances are heterogeneous in nature, their sampling must be carried out with special care by personnel with particular expertise. Each batch must be identified by its own documentation.

14. A reference sample of the plant material is necessary, especially in those cases where the herbal substance is not described in the European Pharmacopoeia or in another Pharmacopoeia of a Member State. Samples of unmilled plant material are required if powders are used.

15. Quality Control personnel must have particular expertise and experience in herbal substances, herbal preparations and/or herbal medicinal products in order to be able to carry out identification tests and recognize adulteration, the presence of fungal growth, infestations, non-uniformity within a delivery of crude material, etc.

16. The identity and quality of herbal substances, herbal preparations and of herbal medicinal products must be determined in accordance with the relevant current European guidance on quality and specifications of herbal medicinal products and traditional herbal medicinal products and, where relevant, to the specific European Pharmacopoeia Monographs.

ANNEX 8

SAMPLING OF STARTING AND PACKAGING MATERIALS

Principle

Sampling is an important operation in which only a small fraction of a batch is taken. Valid conclusions on the whole cannot be based on tests which have been carried out on misrepresentative samples. Correct sampling is thus an essential part of a system of Quality Assurance.

Note: Sampling is dealt with in Chapter 6 of the Guide, sections 6.11. to 6.14. This annex gives additional guidance on the sampling of starting and packaging materials.

Personnel

1. Personnel who take samples must receive initial and ongoing regular training in the disciplines relevant to correct sampling. This training must include:
   - Sampling plans;
   - Written sampling procedures;
   - The techniques and equipment for sampling;
   - The risk of cross-contamination;
   - the precautions to be taken with regard to unstable and/or sterile substances,
   - the importance of considering the visual appearance of materials, containers and labels,
   - the importance of recording any unexpected or unusual circumstances.

Starting materials

2. The identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample. It is allowed to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labelled.

3. This validation must take account of at least the following aspects:
   - the nature and status of the manufacturer and of the supplier and their understanding of the GMP requirements of the Pharmaceutical Industry;
   - the Quality Assurance system of the manufacturer of the starting material;
   - the manufacturing conditions under which the starting material is produced and controlled;
   - the nature of the starting material and the medicinal products in which it will be used.

   Under such a system, it is possible that a validated procedure exempting identity testing of each incoming container of starting material could be accepted for:
   - starting materials coming from a single product manufacturer or plant;
   - starting materials coming directly from a manufacturer or in the manufacturer's sealed container where there is a history of reliability and regular audits of the manufacturer's Quality Assurance system are conducted by the purchaser (the manufacturer of the medicinal product) or by an officially accredited body.

It is improbable that a procedure could be satisfactorily validated for:
- starting materials supplied by intermediaries such as brokers where the source of manufacture is unknown or not audited;
- starting materials for use in parenteral products.

4. The quality of a batch of starting materials may be assessed by taking and testing a representative sample. The samples taken for identity testing could be used for this purpose. The number of samples taken for the preparation of a representative sample must be determined statistically and specified in a sampling plan. The number of individual samples which may be blended to form a composite sample must also be defined, taking into account the nature of the material, knowledge of the supplier and the homogeneity of the composite sample.

Packaging material

5. The sampling plan for packaging materials must take account of at least the following: the quantity received, the quality required, the nature of the material (e.g. primary packaging materials and/or printed packaging materials), the production methods, and what is known of the Quality Assurance system of the packaging materials manufacturer based on audits. The number of samples taken must be determined statistically and specified in a sampling plan.

ANNEX 9

MANUFACTURE OF LIQUIDS, CREAMS AND OINTMENTS

Principle

Liquids, creams and ointments may be particularly susceptible to microbial and other contamination during manufacture. Therefore special measures must be taken to prevent any contamination.

Premises and equipment

1. The use of closed systems for processing and transfer is recommended in order to protect the product from contamination. Production areas where the products or open clean containers are exposed must normally be effectively ventilated with filtered air.
2. Tanks, containers, pipework and pumps must be designed and installed so that they may be readily cleaned and if necessary sanitised. In particular, equipment design must include a minimum of dead-legs or sites where residues can accumulate and promote microbial proliferation.
3. The use of glass apparatus must be avoided wherever possible. High quality stainless steel is often the material of choice for parts coming into contact with the products.

Production

4. The chemical and microbiological quality of the water used in production must be specified and monitored. Care must be taken in the maintenance of water systems in order to avoid the risk of microbial proliferation. After any chemical sanitisation of the water systems, a validated flushing procedure must be followed to ensure that the sanitising agent has been effectively removed.

5. The quality of materials received in bulk tankers must be checked before they are transferred to bulk storage tanks.
6. Care must be taken when transferring materials via pipelines to ensure that they are delivered to their correct destination.
7. Materials likely to shed fibres or other contaminants, like cardboard or wooden pallets, must not enter the areas where products or clean containers are exposed.
8. Care must be taken to maintain the homogeneity of mixtures, suspensions, etc. during filling. Mixing and filling processes must be validated. Special care must be taken at the beginning of a filling process, after stoppages and at the end of the process to ensure that homogeneity is maintained.
9. When the finished product is not immediately packaged, the maximum period of storage and the storage conditions must be specified and adhered to.

ANNEX 10

MANUFACTURE OF PRESSURISED METERED DOSE AEROSOL PREPARATIONS FOR INHALATION

Principle

The manufacture of pressurised aerosol products for inhalation with metering valves requires special consideration because of the particular nature of this pharmaceutical form. It must be done under conditions which minimise microbial and particulate contamination. Assurance of the quality of the valve components and, in the case of suspensions, of uniformity is also of particular importance.

General

1. There are presently two common manufacturing and filling methods as follows:
   a) Two-shot system (pressure filling). The active ingredient is suspended in a high boiling point propellant, the dose is put into the container, the valve is crimped on and the lower boiling point propellant is injected through the valve stem to make up the finished product. The suspension of active ingredient in propellant is kept cool to reduce evaporation loss.
   b) One-shot process (cold filling). The active ingredient is suspended in a mixture of propellants and held either under high pressure or at a low temperature, or both. The suspension is then filled directly into the container in one shot.

Premises and equipment

2. Manufacture and filling must be carried out as far as possible in a closed system.
3. Where products or clean components are exposed, the area must be fed with filtered air, must comply with the requirements of at least a Grade D environment and must be entered through airlocks.

Production and quality control

4. Metering valves for aerosols are more complex pieces of engineering than most items used in pharmaceutical production. Their specifications, sampling and testing must recognize

this. Auditing the Quality Assurance system of the valve manufacturer is of particular importance.

5. All fluids (e.g. liquid or gaseous propellants) must be filtered to remove particles greater than 0.2 micron. An additional filtration where possible immediately before filling is desirable.
6. Containers and valves must be cleaned using a validated procedure corresponding to the use of the product to ensure the absence of any contaminants such as fabrication aids (e.g. lubricants) or undue microbiological contaminants. After cleaning, valves must be kept in clean, closed containers and precautions taken not to introduce contamination during subsequent handling (e.g. while taking samples). Containers must be fed to the filling line in a clean condition or cleaned on line immediately before filling.
7. Precautions must be taken to ensure uniformity of suspensions at the point of fill throughout the filling process.
8. When a two-shot filling process is used, it is necessary to ensure that both shots are of the correct weight in order to achieve the correct composition. For this purpose, 100% weight checking at each stage is often desirable.
9. Controls after filling must ensure the absence of undue leakage. Any leakage test must be performed in a way which avoids microbial contamination or residual moisture.

ANNEX 11

COMPUTERISED SYSTEMS

Principle

This annex applies to all forms of computerised systems used as part of a GMP regulated activities. A computerised system is a set of software and hardware components which together fulfil certain functionalities. The application should be validated; IT infrastructure should be qualified. Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality, process control or quality assurance. There should be no increase in the overall risk of the process.

General

1. Risk Management

Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data integrity and product quality. As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system.

2. Personnel

There should be close cooperation between all relevant personnel (such as Process Owner, System Owner, Qualified Persons) and IT personnel.

3. Suppliers and service providers

3.1 When third parties (e.g. suppliers, service providers) are used e.g. to provide, install, configure, integrate, validate, maintain (e.g. via remote access), modify or retain a computerised system or related service or for data processing, formal agreements must exist between the manufacturer and any third parties, and these agreements should include clear statements of the responsibilities of the third party. IT-departments should be considered analogous.

3.2 The competence and reliability of a supplier are key factors when selecting a product or service provider. The need for an audit should be based on a risk assessment.

3.3 Documentation supplied with commercial off-the-shelf products should be reviewed by regulated users to check that user requirements are fulfilled.

3.4 Quality system and audit information relating to suppliers or developers of software and implemented systems should be made available to inspectors on request.

Project phase

4. Validation

4.1 The validation documentation and reports should cover the relevant steps of the life cycle. Manufacturers should be able to justify their standards, protocols, acceptance criteria, procedures and records based on their risk assessment.

4.2 Validation documentation should include change control records (if applicable) and reports on any deviations observed during the validation process.

4.3 An updated listing of all relevant systems and their GMP functionality (inventory) should be available. For critical systems an updated system description detailing the physical and logical arrangements, data flows and interfaces with other systems or processes, any hardware and software pre-requisites, and security measures should be available.

4.4 User Requirements Specifications should describe the required functions of the computerised system and be based on documented risk assessment and GMP impact. User requirements should be traceable throughout the life-cycle.

4.5 The regulated user should take all reasonable steps, to ensure that the system has been developed in accordance with an appropriate quality management system. The supplier should be assessed appropriately.

4.6 For the validation of bespoke or customised computerised systems there should be a process in place that ensures the formal assessment and reporting of quality and performance measures for all the life-cycle stages of the system.

4.7 Evidence of appropriate test methods and test scenarios should be demonstrated. Particularly, system (process) parameter limits, data limits and error handling should be considered. Automated testing tools and test environments should have documented assessments for their adequacy.

4.8 If data are transferred to another data format or system, validation should include checks that data are not altered in value and/or meaning during this migration process.

Operational phase

5. Data

Computerised systems exchanging data electronically with other systems should include appropriate built-in checks for the correct and secure entry and processing of data, in order to minimize the risks.

6. Accuracy checks

For critical data entered manually, there should be an additional check on the accuracy of the data. This check may be done by a second operator or by validated electronic means. The criticality and the potential consequences of erroneous or incorrectly entered data to a system should be covered by risk management.

7. Data storage

7.1 Data should be secured by both physical and electronic means against damage. Stored data should be checked for accessibility, readability and accuracy. Access to data should be ensured throughout the retention period.

7.2 Regular back-ups of all relevant data should be done. Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically.

8. Printouts

8.1 It should be possible to obtain clear printed copies of electronically stored data.

8.2 For records supporting batch release it should be possible to generate printouts indicating if any of the data has been changed since the original entry.

9. Audit Trails

Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail"). For change or deletion of GMP-relevant data the reason should be documented. Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed.

10. Change and configuration management

Any changes to a computerised system including system configurations should only be made in a controlled manner in accordance with a defined procedure.

11. Periodic evaluation

Computerised systems should be periodically evaluated to confirm that they remain in a valid state and are GMP-compliant. Such evaluations should include, where appropriate, the current range of functionality, deviation records, incidents, problems, upgrade history, performance, reliability, security and validation status reports.

12. Security

12.1 Physical and/or logical controls should be in place to restrict access to computerised system to authorised persons. Suitable methods of preventing unauthorised entry to the system may include the use of keys, pass cards, personal codes with passwords, biometrics, restricted access to computer equipment and data storage areas.

12.2 The extent of security controls depends on the criticality of the computerised system.

12.3 Creation, change, and cancellation of access authorisations should be recorded.

12.4 Management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming or deleting data including date and time.

13. Incident management

All incidents, not only system failures and data errors, should be reported and assessed. The root cause of a critical incident should be identified and should form the basis of corrective and preventive actions.

14. Electronic signature

Electronic records may be signed electronically. Electronic signatures are expected to:

a. have the same impact as hand-written signatures within the boundaries of the company,

b. be permanently linked to their respective record,

c. include the time and date that they were applied.

15. Batch release

When a computerised system is used for recording certification and batch release, the system should allow only Qualified Persons to certify the release of the batches and it should clearly identify and record the person releasing or certifying the batches. This should be performed using an electronic signature.

16. Business continuity

For the availability of computerised systems supporting critical processes, provisions should be made to ensure continuity of support for those processes in the event of a system breakdown (e.g. a manual or alternative system). The time required to bring the alternative arrangements into use should be based on risk and appropriate for a particular system and the business process it supports. These arrangements should be adequately documented and tested.

17. Archiving

Data may be archived. This data should be checked for accessibility, readability and integrity. If relevant changes are to be made to the system (e.g. computer equipment or programs), then the ability to retrieve the data should be ensured and tested.

Glossary

Application: Software installed on a defined platform/hardware providing specific functionality
Bespoke/Customized computerised system: A computerised system individually designed to suit a specific business process
Commercial of the shelf software: Software commercially available, whose fitness for use is demonstrated by a broad spectrum of users.
IT Infrastructure: The hardware and software such as networking software and operation systems, which makes it possible for the application to function.
Life cycle: All phases in the life of the system from initial requirements until retirement including design, specification, programming, testing, installation, operation, and maintenance.
Process owner: The person responsible for the business process.
System owner: The person responsible for the availability, and maintenance of a computerised system and for the security of the data residing on that system.
Third party: Parties not directly managed by the holder of the manufacturing and/or import authorisation.

ANNEX 12

USE OF IONISING RADIATION IN THE MANUFACTURE OF MEDICINAL PRODUCTS

Note: The holder of or applicant for a marketing authorisation for a product which includes irradiation as part of its processing should also refer to the note produced by the Committee for Proprietary Medicinal Products giving guidance on "Ionising radiation in the manufacture of medicinal products".

Introduction

Ionising radiation may be used during the manufacturing process for various purposes including the reduction of bioburden and the sterilisation of starting materials, packaging components or products and the treatment of blood products.

There are two types of irradiation process: Gamma Irradiation from a radioactive source and high energy Electron Irradiation (Beta radiation) from an accelerator.

Gamma irradiation – two different processing modes may be employed:

- Batch mode: the product is arranged at fixed locations around the radiation source and cannot be loaded or unloaded while the radiation source is exposed.
- Continuous mode: an automatic system conveys the products into the radiation cell, past the exposed radiation source along a defined path and at an appropriate speed, and out of the cell.

Electron Irradiation: the product is conveyed past a continuous or pulsed beam of high energy electrons (Beta radiation) which is scanned back and forth across the product pathway.

Responsibilities

1. Treatment by irradiation may be carried out by the pharmaceutical manufacturer or by an operator of a radiation facility under contract (a "contract manufacturer"), both of whom must hold an appropriate manufacturing authorisation.
2. The pharmaceutical manufacturer bears responsibility for the quality of the product including the attainment of the objective of irradiation. The contract operator of the radiation facility bears responsibility for ensuring that the dose of radiation required by the manufacturer is delivered to the irradiation container (i.e. the outermost container in which the products are irradiated).
3. The required dose including justified limits will be stated in the marketing authorization for the product.

Dosimetry

4. Dosimetry is defined as the measurement of the absorbed dose by the use of dosimeters. Both understanding and correct use of the technique is essential for the validation, commissioning and control of the process.
5. The calibration of each batch of routine dosimeters should be traceable to a national or international standard. The period of validity of the calibration should be stated, justified and adhered to.
6. The same instrument should normally be used to establish the calibration curve of the routine dosimeters and to measure the change in their absorbance after irradiation. If a different instrument is used, the absolute absorbance of each instrument should be established.
7. Depending on the type of dosimeter used, due account should be taken of possible causes of inaccuracy including the change in moisture content, change in temperature, time elapsed between irradiation and measurement, and the dose rate.
8. The wavelength of the instrument used to measure the change in absorbance of dosimeters and the instrument used to measure their thickness should be subject to regular checks of calibration at intervals established on the basis of stability, purpose and usage.

Validation of the process

9. Validation is the action of proving that the process, i.e. the delivery of the intended absorbed dose to the product, will achieve the expected results. The requirements for validation are given more fully in the note for guidance on "the use of ionising radiation in the manufacture of medicinal products".
10. Validation should include dose mapping to establish the distribution of absorbed dose within the irradiation container when packed with product in a defined configuration.
11. An irradiation process specification should include at least the following:
    a. details of the packaging of the product;
    b. the loading pattern(s) of product within the irradiation container. Particular care needs to be taken, when a mixture of products is allowed in the irradiation container, that there is no underdosing of dense product or shadowing of other products by dense product. Each mixed product arrangement must be specified and validated;
    c. the loading pattern of irradiation containers around the source (batch mode) or the pathway through the cell (continuous mode);
    d. maximum and minimum limits of absorbed dose to the product [and associated routine dosimetry];

e. maximum and minimum limits of absorbed dose to the irradiation container and associated routine dosimetry to monitor this absorbed dose;

f. other process parameters, including dose rate, maximum time of exposure, number of exposures, etc. When irradiation is supplied under contract at least parts (d) and (e) of the irradiation process specification should form part of that contract.

Commissioning of the plant

General

12. Commissioning is the exercise of obtaining and documenting evidence that the irradiation plant will perform consistently within predetermined limits when operated according to the process specification. In the context of this annex, predetermined limits are the maximum and minimum doses designed to be absorbed by the irradiation container. It must not be possible for variations to occur in the operation of the plant which give a dose to the container outside these limits without the knowledge of the operator.
13. Commissioning should include the following elements:
    a. Design;
    b. Dose mapping;
    c. Documentation;
    d. Requirements for re-commissioning.

Gamma irradiators

Design

14. The absorbed dose received by a particular part of an irradiation container at any specific point in the irradiator depends primarily on the following factors:
    a. The activity and geometry if the source;
    b. The distance from source to container;
    c. The duration of irradiation controlled by the timer setting or conveyor speed;
    d. The composition and density of material, including other products, between the source and the particular part of the container.
15. The total absorbed dose will in addition depend on the path of containers through a continuous irradiator or the loading pattern in a batch irradiator, and on the number of exposure cycles.
16. For a continuous irradiator with a fixed path or a batch irradiator with a fixed loading pattern, and with a given source strength and type of product, the key plant parameter controlled by the operator is conveyor speed or timer setting.

Dose mapping

17. For the dose mapping procedure, the irradiator should be filled with irradiation containers packed with dummy products or a representative product of uniform density. Dosimeters should be placed throughout a minimum of three loaded irradiation containers which are passed through the irradiator, surrounded by similar containers or dummy products. If the product is not uniformly packed, dosimeters should be placed in a larger number of containers.
18. The positioning of dosimeters will depend on the size of the irradiation container. For example, for containers up to 1 x 1 x 0.5 m, a three-dimensional 20 cm grid throughout the container including the outside surfaces might be suitable. If the expected positions of the minimum and maximum dose are known from a previous irradiator performance characterisation, some dosimeters could be removed from regions of average dose and replaced to form a 10 cm grid in the regions of extreme dose.
19. The results of this procedure will give minimum and maximum absorbed doses in the product and on the container surface for a given set of plant parameters, product density and loading pattern.

20. Ideally, reference dosimeters should be used for the dose mapping exercise because of their greater precision. Routine dosimeters are permissible but it is advisable to place reference dosimeters beside them at the expected positions of minimum and maximum dose and at the routine monitoring position in each of the replicate irradiation containers. The observed values of dose will have an associated random uncertainty which can be estimated from the variations in replicate measurements.
21. The minimum observed dose, as measured by the routine dosimeters, necessary to ensure that all irradiation containers receive the minimum required dose will be set in the knowledge of the random variability of the routine dosimeters used.
22. Irradiator parameters should be kept constant, monitored and recorded during dose mapping. The records, together with the dosimetry results and all other records generated should be retained.

Electron beam irradiators

Design

23. The absorbed dose received by a particular portion of an irradiated product depends primarily on the following factors:
    a. the characteristics of the beam, which are: electron energy, average beam current, scan width and scan uniformity;
    b. the conveyor speed;
    c. the product composition and density;
    d. the composition, density and thickness of material between the output window and the particular portion of product;
    e. the output window to container distance.
24. Key parameters controlled by the operator are the characteristics of the beam and the conveyor speed.

Dose mapping

25. For the dose mapping procedure, dosimeters should be placed between layers of homogeneous absorber sheets making up a dummy product, or between layers of representative products of uniform density, such that at least ten measurements can be made within the maximum range of the electrons. Reference should also be made to sections 18 to 21.
26. Irradiator parameters should be kept constant, monitored and recorded during dose mapping. The records, together with the dosimetry results and all other records generated should be retained.

Re-commissioning

27. Commissioning should be repeated if there is a change to the process or the irradiator which could affect the dose distribution to the irradiation container (e.g. change of source pencils). The extent to re-commissioning depends on the extent of the change in the irradiator or the load that has taken place. If in doubt, re-commission.

Premises

28. Premises should be designed and operated to segregate irradiated from non-irradiated containers to avoid their cross-contamination. Where materials are handled within closed irradiation containers, it may not be necessary to segregate pharmaceutical from nonpharmaceutical materials, provided there is no risk of the former being contaminated by the latter. Any possibility of contamination of the products by radionuclide from the source must be excluded.

Processing

29. Irradiation containers should be packed in accordance with the specified loading pattern(s) established during validation.
30. During the process, the radiation dose to the irradiation containers should be monitored using validated dosimetry procedures. The relationship between this dose and the dose absorbed by the product inside the container must have been established during process validation and plant commissioning.
31. Radiation indicators should be used as an aid to differentiating irradiated from non-irradiated containers. They should not be used as the sole means of differentiation or as an indication of satisfactory processing.
32. Processing of mixed loads of containers within the irradiation cell should only be done when it is known from commissioning trials or other evidence that the radiation dose received by individual containers remains within the limits specified.
33. When the required radiation dose is by design given during more than one exposure or passage through the plant, this should be with the agreement of the holder of the marketing authorisation and occur within a predetermined time period. Unplanned interruptions during irradiation should be notified to the holder of the marketing authorisation if this extends the irradiation process beyond a previously agreed period.
34. Non-irradiated products must be segregated from irradiated products at all times. Methods of doing this include the use of radiation indicators (Section 31.) and appropriate design of premises (Section 28.).

Gamma irradiators

35. For continuous processing modes, dosimeters should be placed so that at least two are exposed in the irradiation at all times.
36. For batch modes, at least two dosimeters should be exposed in positions related to the minimum dose position.
37. For continuous process modes, there should be a positive indication of the correct position of the source and an interlock between source position and conveyor movement. Conveyor speed should be monitored continuously and recorded.
38. For batch process modes source movement and exposure times for each batch should be monitored and recorded.
39. For a given desired dose, the timer setting or conveyor speed requires adjustment for source decay and source additions. The period of validity of the setting or speed should be recorded and adhered to.

Electron beam irradiators

40. A dosimeter should be placed on every container.
41. There should be continuous recording of average beam current, electron energy, scan-width and conveyor speed. These variables, other than conveyor speed, need to be controlled within the defined limits established during commissioning since they are liable to instantaneous change.

Documentation

42. The numbers of containers received, irradiated and dispatched should be reconciled with each other and with the associated documentation. Any discrepancy should be reported and resolved.
43. The irradiation plant operator should certify in writing the range of doses received by each irradiated container within a batch or delivery.
44. Process and control records for each irradiation batch should be checked and signed by a nominated responsible person and retained. The method and place of retention should be agreed between the plant operator and the holder of the marketing authorisation.

45. The documentation associated with the validation and commissioning of the plant should be retained for one year after the expiry date or at least five years after the release of the last product processed by the plant, whichever is the longer.

Microbiological monitoring

46. Microbiological monitoring is the responsibility of the pharmaceutical manufacturer. It may include environmental monitoring where product is manufactured and pre-irradiation monitoring of the product as specified in the marketing authorisation.

ANNEX 13

MANUFACTURE OF INVESTIGATIONAL MEDICINAL PRODUCTS

Principle

Investigational medicinal products should be produced in accordance with the principles and the detailed guidelines of Good Manufacturing Practice for Medicinal Products (The Rules Governing Medicinal Products in The European Community, Volume IV). Other guidelines published by the European Commission should be taken into account where relevant and as appropriate to the stage of development of the medicinal product. Procedures need to be flexible to provide for changes as knowledge of the process increases, and appropriate to the stage of development of the product.

In clinical trials there may be added risk to participating subjects compared to patients treated with marketed products. The application of GMP to the manufacture of investigational medicinal products is intended to ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture. Equally, it is intended to ensure that there is consistency between batches of the same investigational medicinal product used in the same or different clinical trials, and that changes during the development of an investigational medicinal product are adequately documented and justified.

The production of investigational medicinal products involves added complexity in comparison to marketed products by virtue of the lack of fixed routines, variety of clinical trial designs, consequent packaging designs, and the need, often, for randomisation and blinding and increased risk of product cross-contamination and mix up. Furthermore, there may be incomplete knowledge of the potency and toxicity of the product and a lack of full process validation, or, marketed products may be used which have been re-packaged or modified in some way.

These challenges require personnel with a thorough understanding of, and training in, the application of GMP to investigational medicinal products. Co-operation is required with trial sponsors who undertake the ultimate responsibility for all aspects of the clinical trial including the quality of investigational medicinal products.

The increased complexity in manufacturing operations requires a highly effective quality system.

The Annex also includes guidance on ordering, shipping, and returning clinical supplies, which are at the interface with, and complementary to, guidelines on Good Clinical Practice.

Note:

Non-investigational medicinal product[8]

Products other than the test product, placebo or comparator may be supplied to subjects participating in a trial. Such products may be used as support or escape medication for preventative, diagnostic or therapeutic reasons and/or needed to ensure that adequate medical care is provided for the subject. They may also be used in accordance with the protocol to induce a

[8] Further information can be found in the European Commission's Guidance on Investigational Medicinal Products (IMPs) and other Medicinal Products used in Clinical Trials

physiological response. These products do not fall within the definition of investigational medicinal products and may be supplied by the sponsor, or the investigator.
The sponsor should ensure that they are in accordance with the notification/request for authorisation to conduct the trial and that they are of appropriate quality for the purposes of the trial taking into account the source of the materials, whether or not they are the subject of a marketing authorisation and whether they have been repackaged. The advice and involvement of a Qualified Person is recommended in this task.

Manufacturing authorisation and reconstitution

Both the total and partial manufacture of investigational medicinal products, as well as the various processes of dividing up, packaging or presentation, is subject to the authorization referred to in Article 13(1) Directive 2001/20/EC, cf. Article 9(1) Directive 2005/28/EC. This authorisation, however, shall not be required for reconstitution under the conditions set out in Article 9(2) Directive 2005/28/EC. For the purpose of these provisions, reconstitution shall be understood as a simple process of:

- dissolving or dispersing the investigational medicinal product for administration of the product to a trial subject,
- or, diluting or mixing the investigational medicinal product(s) with some other substance(s) used as a vehicle for the purposes of administering it,

Reconstitution is not mixing several ingredients, including the active substance, together to produce the investigational medicinal product.
An investigational medicinal product must exist before a process can be defined as reconstitution. The process of reconstitution has to be undertaken as soon as practicable before administration. This process has to be defined in the clinical trial application / IMP dossier and clinical trial protocol, or related document, available at the site.

Glossary

„Blinding"

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).
In relation to an investigational medicinal product, blinding shall mean the deliberate disguising of the identity of the product in accordance with the instructions of the sponsor. Unblinding shall mean the disclosure of the identity of blinded products.

Clinical trial

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its/their safety and/or efficacy.

Comparator product

An investigational or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the main investigator.

Investigational medicinal product

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including medicinal products with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

Manufacturer/importer of Investigational Medicinal Products

Any person engaged in activities for which the authorisation referred to in Article 48 of the Order of the Minister of Public Health No. 904/2006 is required.

Order

Instruction to process, package and/or ship a certain number of units of investigational medicinal product(s).

Product specification file

A reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product.

Randomisation

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Randomisation code

A listing in which the treatment assigned to each subject from the randomisation process is identified.

Shipping

The operation of packaging for shipment and sending of ordered medicinal products for clinical trials.

Sponsor

An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

QUALITY MANAGEMENT

1. The Quality System, designed, set up and verified by the manufacturer or importer, should be described in written procedures available to the sponsor, taking into account the GMP principles and guidelines applicable to investigational medicinal products.
2. The product specifications and manufacturing instructions may be changed during development but full control and traceability of the changes should be maintained.

PERSONNEL

3. All personnel involved with investigational medicinal products should be appropriately trained in the requirements specific to these types of product.
   Even in cases where the number of staff involved is small, there should be, for each batch, separate people responsible for production and quality control.
4. The Qualified Person should ensure that there are systems in place that meet the requirements of GMP and should have a broad knowledge of pharmaceutical development and clinical trial processes. Guidance for the Qualified Person in connection with the certification of investigational medicinal products is given in paragraphs 38 to 41.

PREMISES AND EQUIPMENT

5. The toxicity, potency and sensitising potential may not be fully understood for investigational medicinal products and this reinforces the need to minimise all risks of cross-contamination. The design of equipment and premises, inspection / test methods and acceptance limits to be used after cleaning should reflect the nature of these risks. Consideration should be given to campaign working where appropriate. Account should be taken of the solubility of the product in decisions about the choice of cleaning solvent.

DOCUMENTATION

Specifications and instructions

6. Specifications (for starting materials, primary packaging materials, intermediate, bulk products and finished products), manufacturing formulae and processing and packaging instructions should be as comprehensive as possible given the current state of knowledge. They should be periodically re-assessed during development and updated as necessary. Each new version should take into account the latest data, current technology used, regulatory and pharmacopoeial requirements, and should allow traceability to the previous document. Any changes should be carried out according to a written procedure, which should address any implications for product quality such as stability and bio equivalence.
7. Rationales for changes should be recorded and the consequences of a change on product quality and on any ongoing clinical trials should be investigated and documented[9].

Order

8. The order should request the processing and/or packaging of a certain number of units and/or their shipping and be given by or on behalf of the sponsor to the manufacturer. It should be in writing (though it may be transmitted by electronic means), and precise enough to avoid any ambiguity. It should be formally authorised and refer to the Product Specification File and the relevant clinical trial protocol as appropriate.

Product Specification File

9. The Product Specification File (see Glossary) should be continually updated as development of the product proceeds, ensuring appropriate traceability to the previous versions. It should include, or refer to, the following documents:
    - Specifications and analytical methods for starting materials, packaging materials, intermediate/bulk/finished products;
    - Manufacturing methods;
    - In-process testing and methods;
    - Approved label copy;
    - Relevant clinical trial protocols and randomisation codes, as appropriate;
    - Relevant technical agreements with contract givers, as appropriate;
    - Stability data;
    - Storage and shipment conditions.
10. The above listing is not intended to be exclusive or exhaustive. The contents will vary depending on the product and stage of development. The information should form the basis for assessment of the suitability for certification and release of a particular batch by the Qualified Person and should therefore be accessible to him/her. Where different manufacturing steps are carried out at different locations under the responsibility of

[9] Guidance on changes that require the request of a substantial amendment to the IMP dossier submitted to the Competent Authorities is given in the CHMP guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials

different Qualified Persons, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations.

Manufacturing formulae and processing instructions

11. For every manufacturing operation or supply there should be clear and adequate written instructions and written records. Where an operation is not repetitive it may not be necessary to produce Master Formulae and Processing Instructions. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture once the marketing authorisation is granted. The information in the Product Specification File should be used to produce the detailed written instructions on processing, packaging, quality control testing, storage conditions and shipping**.**

Packaging instructions

12. Investigational medicinal products are normally packed in an individual way for each subject included in the clinical trial. The number of units to be packaged should be specified prior to the start of the packaging operations, including units necessary for carrying out quality control and any retention samples to be kept. Sufficient reconciliations should take place to ensure the correct quantity of each product required has been accounted for at each stage of processing.

Processing, testing and packaging batch records

13. Batch records should be kept in sufficient detail for the sequence of operations to be accurately determined. These records should contain any relevant remarks which justify the procedures used and any changes made, enhance knowledge of the product and develop the manufacturing operations.
14. Batch manufacturing records should be retained at least for the periods specified in The Order of the Minister of Public Health No. 905/2006.

Production

Packaging materials

15. Specifications and quality control checks should include measures to guard against unintentional unblinding due to changes in appearance between different batches of packaging materials**.**

Manufacturing operations

16. During development critical parameters should be identified and in-process controls primarily used to control the process. Provisional production parameters and in-process controls may be deduced from prior experience, including that gained from earlier development work. Careful consideration by key personnel is called for in order to formulate the necessary instructions and to adapt them continually to the experience gained in production. Identified and controlled parameters should be justifiable based on knowledge available at the time.
17. Production processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production but premises and equipment are expected to be qualified. For sterile products, the validation of sterilising processes should be of the same standard as for products authorised for marketing. Likewise, when required, virus inactivation/removal and that of other impurities of biological origin should be demonstrated, to assure the safety of biotechnologically derived products, by following the scientific principles and techniques defined in the available guidance in this area.
18. Validation of aseptic processes presents special problems when the batch size is small; in these cases the number of units filled may be the maximum number filled in production. If practicable, and otherwise consistent with simulating the process, a larger number of units should be filled with media to provide greater confidence in the results obtained. Filling

and sealing is often a manual or semi-automated operation presenting great challenges to sterility so enhanced attention should be given to operator training, and validating the aseptic technique of individual operators.

Principles applicable to comparator products

19. If a product is modified, data should be available (e.g. stability, comparative dissolution, bioavailability) to demonstrate that these changes do not significantly alter the original quality characteristics of the medicinal product.
20. The expiry date stated for the comparator product in its original packaging might not be applicable to the product where it has been repackaged in a different container that may not offer equivalent protection, or be compatible with the product. A suitable use-by date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the article may be subjected, should be determined by or on behalf of the sponsor. Such a date should be justified and must not be later than the expiry date of the original package. There should be compatibility of expiry dating and clinical trial duration.

Blinding operations

21. Where products are blinded, systems should be in place to ensure that the blind is achieved and maintained while allowing for identification of "blinded" products when necessary, including the batch numbers of the products before the blinding operation. Rapid identification of product should also be possible in an emergency.

Randomisation code

22. Procedures should describe the generation, security**,** distribution, handling and retention of any randomisation code used for packaging investigational products, and code-break mechanisms. Appropriate records should be maintained.

Packaging

23. During packaging of investigational medicinal products, it may be necessary to handle different products on the same packaging line at the same time. The risk of product mix up must be minimised by using appropriate procedures and/or, specialised equipment as appropriate and relevant staff training.
24. Packaging and labelling of investigational medicinal products are likely to be more complex and more liable to errors (which are also harder to detect) than for marketed products, particularly when "blinded" products with similar appearance are used. Precautions against mis-labelling such as label reconciliation, line clearance, in process control checks by appropriately trained staff should accordingly be intensified.
25. The packaging must ensure that the investigational medicinal product remains in good condition during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.

Labelling

26. Table 1 summarises the contents of Articles 26-30 that follow. Labelling should comply with the requirements of the Order of the Minister of Public Health No. 905/2006. The following information should be included on labels, unless its absence can be justified, e.g. use of a centralised electronic randomisation system:
    a) name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding);
    b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;
    c) the batch and/or code number to identify the contents and packaging operation;

d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
e) the trial subject identification number/treatment number and where relevant, the visit number;
f) the name of the investigator (if not included in (a) or (d));
g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product);
h) "For clinical trial use only" or similar wording;
i) the storage conditions;
j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity.
k) "keep out of reach of children" except when the product is for use in trials where the product is not taken home by subjects.

27. The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times.

28. Particulars should appear in the official language(s) of the country in which the investigational medicinal product is to be used. The particulars listed in Article 26 should appear on the primary packaging and on the secondary packaging (except for the cases described in Articles 29 and 30). The requirements with respect to the contents of the label on the primary and outer packaging are summarised in Table 1. Other languages may be included.

29. When the product is to be provided to the trial subject or the person administering the medication within a primary package together with secondary packaging that is intended to remain together, and the secondary packaging carries the particulars listed in Paragraph 26, the following information shall be included on the label of the primary package (or any sealed dosing device that contains the primary packaging):
a) name of sponsor, contract research organisation or investigator;
b) pharmaceutical dosage form, route of administration (may be excluded for oral solid dose forms), quantity of dosage units and in the case of open label trials, the name/identifier and strength/potency;
c) batch and/or code number to identify the contents and packaging operation;
d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
e) the trial subject identification number/treatment number and where relevant, the visit number.

30. If the primary packaging takes the form of blister packs or small units such as ampoules on which the particulars required in Paragraph 26 cannot be displayed, secondary packaging should be provided bearing a label with those particulars. The primary packaging should nevertheless contain the following:
a) Name of sponsor, contract research organisation or investigator;
b) route of administration (may be excluded for oral solid dose forms) and in the case of open label trials, the name/identifier and strength/potency;
c) batch and/or code number to identify the contents and packaging operation;
d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
e) the trial subject identification number/treatment number and where relevant, the visit number.

31. Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings and/or handling instructions may be displayed.

32. For clinical trials with the characteristics identified in Chapter XV of the Order of the Minister of Public Health No. 904/2006, the following particulars should be added to the original container but should not obscure the original labelling:
    i) name of sponsor, contract research organisation or investigator;
    ii) trial reference code allowing identification of the trial site, investigator and trial subject.
33. If it becomes necessary to change the use-by date, an additional label should be affixed to the investigational medicinal product. This additional label should state the new use-by date and repeat the batch number; it may be superimposed on the old use-by date, but for quality control reasons, not on the original batch number. This operation should be performed at an appropriately authorised manufacturing site. However, when justified, it may be performed at the investigational site by or under the supervision of the clinical trial site pharmacist, or other healthcare professional in accordance with national regulations. Where this is not possible, it may be performed by the clinical trial monitor(s) who should be appropriately trained. The operation should be performed in accordance with GMP principles, specific and standard operating procedures and under contract, if applicable, and should be checked by a second person. This additional labelling should be properly documented in both the trial documentation and in the batch records.

QUALITY CONTROL

34. As processes may not be standardised or fully validated, testing takes on more importance in ensuring that each batch meets its specification.
35. Quality control should be performed in accordance with the Product Specification File and in accordance with the information notified pursuant to Article 37 of the Order of the Minister of Public Health No. 904/2006. Verification of the effectiveness of blinding should be performed and recorded.
36. Samples are retained to fulfill two purposes; firstly to provide a sample for analytical testing and secondly to provide a specimen of the finished product. Samples may therefore fall into two categories:
    Reference sample: a sample of a batch of starting material, packaging material, product contained in its primary packaging or finished product which is stored for the purpose of being analysed should the need arise. Where stability allows, reference samples from critical intermediate stages (e.g. those requiring analytical testing and release) or intermediates, which are transported outside of the manufacturer's control, should be kept.
    Retention sample: a sample of a packaged unit from a batch of finished product for each packaging run/trial period. It is stored for identification purposes. For example, presentation, packaging, labeling, leaflet, batch number, expiry date should the need arise. In many instances the reference and retention samples will be presented identically, i.e. as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable. Reference and retention samples of investigational medicinal product, including blinded product should be kept for at least two years after completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer.
    Consideration should be given to keeping retention samples until the clinical report has been prepared to enable confirmation of product identity in the event of, and as part of an investigation into inconsistent trial results.
37. The storage location of Reference and Retention samples should be defined in a Technical Agreement between the sponsor and manufacturer(s) and should allow timely access by the competent authorities.
    Reference samples of finished product should be stored within the EEA or in a third country where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the investigational medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the

Community. In exceptional circumstances the reference samples of the finished product may be stored by the manufacturer in another third country, in which case this should be justified, and documented in a technical agreement between the sponsor, importer in the EEA and that third country manufacturer.

The reference sample should be of sufficient size to permit the carrying out, on, at least, two occasions, of the full analytical controls on the batch in accordance with the IMP dossier submitted for authorisation to conduct the clinical trial.

In the case of *retention samples*, it is acceptable to store information related to the final packaging as written or electronic records if such records provide sufficient information. In the case of the latter, the system should comply with the requirements of Annex 11.

RELEASE OF BATCHES

38. Release of investigational medicinal products (see paragraph 43) should not occur until after the Qualified Person has certified that the requirements of Article 50 (1) of the Order of the Minister of Public Health No. 904/2006 have been met (see paragraph 39). The Qualified Person should take into account the elements listed in paragraph 40 as appropriate.

39. The duties of the Qualified Person in relation to investigational medicinal products are affected by the different circumstances that can arise and are referred to below. Table 2 summarises the elements that need to be considered for the most common circumstances:

    a) Product manufactured within EU but not subject to an EU marketing authorisation: the duties are laid down in article 50 (1) a) of the Order of the Minister of Public Health No. 904/2006.

    b) Product sourced from the open market within EU in accordance with Article 791 b) of Law No. 95/2005, Title XVII – The medicinal product and subject to an EU marketing authorisation, regardless of manufacturing origin: the duties are as described above, however, the scope of certification can be limited to assuring that the products are in accordance with the notification/request for authorisation to conduct the trial and any subsequent processing for the purpose of blinding, trial-specific packaging and labelling. The Product Specification File will be similarly restricted in scope (see 9).

    c) Product imported directly from a 3rd country: the duties are laid down in article 50 (1) of the Order of the Minister of Public Health No. 904/2006. Where investigational medicinal products are imported from a 3rd country and they are subject to arrangements concluded between the Community and that country, such as a Mutual Recognition Agreement (MRA), equivalent standards of Good Manufacturing Practice apply provided any such agreement is relevant to the product in question. In the absence of an MRA, the Qualified Person should determine that equivalent standards of Good Manufacturing Practice apply through knowledge of the quality system employed at the manufacturer. This knowledge is normally acquired through audit of the manufacturer's quality systems. In either case, the Qualified Person may then certify on the basis of documentation supplied by the 3rd country manufacturer (see Section 40).

    d) For imported comparator products where adequate assurance cannot be obtained in order to certify that each batch has been manufactured in accordance with equivalent standards of Good Manufacturing Practice, the duty of the Qualified Person is defined in article 50 (1) c) of the Order of the Minister of Public Health No. 904/2006.

40. Assessment of each batch for certification prior to release may include as appropriate:

    - batch records, including control reports, in-process test reports and release reports demonstrating compliance with the product specification file, the order, protocol and randomisation code. These records should include all deviations or planned changes, and

any consequent additional checks or tests, and should be completed and endorsed by the staff authorised to do so according to the quality system;
- production conditions;
- the validation status of facilities, processes and methods;
- examination of finished packs;
- where relevant, the results of any analyses or tests performed after importation;
- stability reports;
- the source and verification of conditions of storage and shipment;
- audit reports concerning the quality system of the manufacturer;
- Documents certifying that the manufacturer is authorised to manufacture investigational medicinal products or comparators for export by the appropriate authorities in the country of export;
- where relevant, regulatory requirements for marketing authorisation, GMP standards applicable and any official verification of GMP compliance;
- all other factors of which the QP is aware that are relevant to the quality of the batch.

The relevance of the above elements is affected by the country of origin of the product, the manufacturer, and the marketed status of the product (with or without a marketing authorisation, in the EU or in a third country) and its phase of development.

The sponsor should ensure that the elements taken into account by the qualified person when certifying the batch are consistent with the information notified pursuant to Article 37 of the Order of the Minister of Public Health No. 904/2006 (see also section 44).

41. Where investigational medicinal products are manufactured and packaged at different sites under the supervision of different Qualified Persons, the recommendations listed in Annex 16 to the GMP Guide should be followed as applicable.

42. Where, permitted in accordance with local regulations, packaging or labelling is carried out at the investigator site by, or under the supervision of a clinical trials pharmacist, or other health care professional as allowed in those regulations, the Qualified Person is not required to certify the activity in question. The sponsor is nevertheless responsible for ensuring that the activity is adequately documented and carried out in accordance with the principles of GMP and should seek the advice of the Qualified Person in this regard.

SHIPPING

43. Investigational medicinal products should remain under the control of the sponsor until after completion of a two-step procedure: certification by the Qualified Person; and release by the sponsor for use in a clinical trial following fulfilment of the requirements of Article 9 (Commencement of a clinical trial) of Directive 2001/20/EC. Both steps should be recorded[10] and retained in the relevant trial files held by or on behalf of the sponsor. The Sponsor should ensure that the details set out in the clinical trial application and considered by the Qualified Person are consistent with what is finally accepted by the Competent Authorities. Suitable arrangements to meet this requirement should be established. In practical terms, this can best be achieved through a change control process for the Product Specification File and defined in a Technical Agreement between the QP and the Sponsor.

44. Shipping of investigational products should be conducted according to instructions given by or on behalf of the sponsor in the shipping order.

45. De-coding arrangements should be available to the appropriate responsible personnel before investigational medicinal products are shipped to the investigator site.

46. A detailed inventory of the shipments made by the manufacturer or importer should be maintained. It should particularly mention the addressees' identification.

47. Transfers of investigational medicinal products from one trial site to another should remain the exception. Such transfers should be covered by standard operating procedures. The

[10] A harmonised format for batch certification to facilitate movement between Member States is provided in Annex 3.

product history while outside of the control of the manufacturer, through for example, trial monitoring reports and records of storage conditions at the original trial site should be reviewed as part of the assessment of the product's suitability for transfer and the advice of the Qualified person should be sought. The product should be returned to the manufacturer, or another authorised manufacturer, for re-labelling, if necessary, and certification by a Qualified Person. Records should be retained and full traceability ensured.

COMPLAINTS

48. The conclusions of any investigation carried out in relation to a complaint which could arise from the quality of the product should be discussed between the manufacturer or importer and the sponsor (if different). This should involve the Qualified Person and those responsible for the relevant clinical trial in order to assess any potential impact on the trial, product development and on subjects.

RECALLS AND RETURNS

Recalls

49. Procedures for retrieving investigational medicinal products and documenting this retrieval should be agreed by the sponsor, in collaboration with the manufacturer or importer where different. The investigator and monitor need to understand their obligations under the retrieval procedure.
50. The Sponsor should ensure that the supplier of any comparator or other medication to be used in a clinical trial has a system for communicating to the Sponsor the need to recall any product supplied.

Returns

51. Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in approved written procedures.
52. Returned investigational medicinal products should be clearly identified and stored in an appropriately controlled, dedicated area. Inventory records of the returned medicinal products should be kept.

Destruction

53. The Sponsor is responsible for the destruction of unused and/or returned investigational medicinal products. Investigational medicinal products should therefore not be destroyed without prior written authorisation by the Sponsor.
54. The delivered, used and recovered quantities of medicinal product should be recorded, reconciled and verified by or on behalf of the sponsor for each trial site and each trial period. Destruction of unused investigational medicinal products should be carried out for a given trial site or a given trial period only after any discrepancies have been investigated and satisfactorily explained and the reconciliation has been accepted. Recording of destruction operations should be carried out in such a manner that all operations may be accounted for. The records should be kept by the Sponsor.
55. When destruction of investigational medicinal products takes place a dated certificate of, or receipt for destruction, should be provided to the sponsor. These documents should clearly identify, or allow traceability to, the batches and/or patient numbers involved and the actual quantities destroyed.

TABLE 1. SUMMARY OF LABELLING DETAILS (point 26 to 30)

a) name, address and telephone number of the sponsor,
contract research organization or

investigator (the main contact for information on the product, clinical trial and emergency unblinding);

b) pharmaceutical dosage, route of administration, quantity of dosage units, and in the case of open trials, and strength/potency;

c) the batch and/or code number to identify the contents and packaging operation;

d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

e) the trial subject identification number/ treatment number and, where relevant, the visit number;

f) the name of the investigator [if not included in a) or d)]

g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product);

h) ,,for clinical trial use only" or similar wording;

i) the storage conditions;

j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity;

k) ,,keep out of reach of children" when the product is for use in trials where the product is not taken home by subjects.

GENERAL CASE

For both the primary and name/identifier secondary packaging (point 26)

Particulars a[4] to k

PRIMARY PACKAGE

Where primary and secondary packaging remain together throughout (point 29)[5]

a[6] b[7] c d e

PRIMARY PACKAGE

Blisters or small packaging units (point 30)[5]

a[6] b[7,8] c d e

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[4] The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label where the subject has been given a leaflet or card which provides these details and has been instructed to keep this in their possession at all times (§ 27).

[5] When the outer packaging carries the particulars listed in Article 26.

[6] The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not be included.

[7] Route of administration may be excluded for oral solid dose forms.

[8] The pharmaceutical dosage form and quantity of dosage units may be omitted.

TABLE 2: BATCH RELEASE OF INVESTIGATIONAL MEDICINAL PRODUCTS

ELEMENTS TO BE TAKEN INTO ACCOUNT (3)	PRODUCTS AVAILABLE IN THE EU		PRODUCT IMPORTED FROM A THIRD COUNTRY		
	Product manufactured in EU without MA	Product with MA and available on EU market	Product without any MA in EU	Product with a EU in MA	Comparator where documentation certifying that each batch has been manufactured in conditions at least equivalent to those laid down in Law No. 95/2006, Title XVII - The medicinal product.
BEFORE CLINICAL TRIAL PROCESSING					
a) Shipping and storage conditions	Yes				
b) All relevant factors[1] showing that each batch has been manufactured and released in accordance with Law No. 95/2006, Title XVII – The medicinal product or GMP standards at least equivalent to those laid down in Law No. 95/2006, Title XVII – The medicinal product	Yes -		(2) Yes		
c) Documentation showing that each batch has been released within the EU in accordance with GMP requirements (see Law No. 95/2006, Title XVII – The medicinal product, Art. 760) or documentation showing that the product is available on the EU market and has been procured in accordance with Art. 791 b) of Law No. 95/2006, Title XVII - The medicinal product		Yes			
d) Documentation showing that the product is available on the local market and documentation to establish confidence in the local regulatory requirements for marketing authorisation and release for local use.					Yes
e) Results of all analysis, tests and checks performed to assess the quality of the imported batch according to: the requirements of the MA (see Law No. 95/2006, Title XVII – The medicinal product, Art. 760 (1) b)), or the Product Specification File, article 37 (Submission to the regulatory			-	Yes	-

authorities) of the Order of the Minister of Public Health No. 904/2006.		Yes Yes -	- Yes	Yes Yes
AFTER CLINICAL TRIAL PROCESSING				
f) In addition to the assessment before clinical trial processing, all further relevant factors (1) showing that each batch has been processed for the purposes of blinding, trial-specific packaging, labelling and testing in accordance with: Law No. 95/2006, Title XVII – The medicinal product, or GMP standards at least equivalent to those laid down in Law No. 95/2006, Title XVII – The medicinal product.	Yes -	(2) Yes		

(1) These factors are summarized in section 40.
(2) In case of a Mutual Recognition Agreement or a similar agreement related to the medicinal products concerned, GMP-equivalent standards shall be applied.
(3) In all cases, the information notified due to Art. 37 of Order of the Minister of Public Health No. 904/2006 should be compliant with the elements considered by the QP responsible with batch certification prior to release.

Annex 3

[LETTERHEAD OF THE MANUFACTURER]
Content of the Batch Certificate
Referred to in Art. 50 (1) of the Order of the Minister of Public Health No. 904/2006

i. Name of product(s)/product identifier(s) as referred to in the clinical trial application, where applicable
ii. EudraCT No(s) and sponsor protocol code number, when available.
iii. Strength
Identity (name) and amount per unit dose for all active substance(s) for each IMP (including placebo). The manner in which this information is provided should not unblind the study.
iv. Dosage form (pharmaceutical form)
v. Package size (size of container) and type (e.g. vials, bottles, blisters etc.).
vi. Lot/batch number
vii. Expiry/retest/use by date
viii. Name and address of manufacturer where the Qualified Person issuing the certificate is located.
ix. Manufacturing Authorisation number for the site listed under item 8.
x. Comments/remarks
xi. Any additional information considered relevant by the QP.
xii. Certification statement
xiii. "I hereby certify that this batch complies with the requirements of Article 50 (1) of Order of the Minister of Public Health No. 904/2006"
xiv. Name of the QP signing the certificate
xv. Signature
xvi. Date of signature

Explanatory note

Investigational medicinal products may not be used in a clinical trial in a member state of the European Economic Area until the completion of the two-step procedure referred to in section 43 of this Annex. The first step is the certification of each batch by the Qualified Person of the manufacturer or importer that the provisions of Article 50 (1) of the Order of the Minister of Public Health No. 904/2006 and documented in accordance with Art. 52 of the same Order. According to the Order of the Minister of Public Health No. 904/2006 and documented in accordance with Art. 52 of the same Order. In accordance with the Order of the Minister of Public Health No. 904/2006, a batch of investigational medicinal product shall not have to undergo further checks in relation to the provisions of article 50 (a), (b) or (c) of the same Order when it moves between Member States accompanied by batch certification signed by the Qualified Person. In order to facilitate the free movement of investigational medicinal products between Member States the content of these certificates should be in accordance with the above harmonised format. This format may also be used to certify batches destined for use within the Member State of the manufacturer or importer.

ANNEX 14

MANUFACTURE OF MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD OR HUMAN PLASMA

Glossary

Blood

Blood, as referred to in Law No. 282/2005 (Annex 1), means whole blood collected from a donor and processed either for transfusion or for further manufacturing.

Blood component

A blood component, as referred to in Law No. 282/2005 (Annex 1), means a therapeutic constituent of blood (red cells, white cells, platelets and plasma) that can be prepared by various methods.

Blood establishment

A blood establishment, as referred to in Law No. 282/2005 (Annex 1), is any structure or body that is responsible for any aspect of the collection and testing of human blood and blood components, whatever their intended purpose, and their processing, storage and distribution when intended for transfusion. While this definition does not include hospital blood banks, it is understood to include centres where apheresis of plasma is performed.

Blood products

A blood product, as referred to in Law No. 282/2005 (Annex 1), means any therapeutic product derived from human blood or plasma.

Fractionation, fractionation plant

Fractionation is the manufacturing process in a plant (fractionation plant) during which plasma components are separated/purified by various physical and chemical methods such as e.g. precipitation, chromatography.

Good Practice Guidelines

Provide interpretation on the Community standards and specifications defined for quality systems in blood establishments established in the Order of the Minister of Public Health No. 1132/2007[11].

Medicinal products derived from human blood or human plasma

Medicinal products derived from human blood or human plasma, as referred to in Law No. 95/2006, Title XVII (Art. 695, No. 9), are medicinal products based on blood constituents which are prepared industrially by public or private establishments.

[11] At the time of publication of this Annex, the adoption of the Good Manufacturing Practice guidelines by the European Commission was still pending

Plasma for fractionation

Plasma for fractionation is the liquid part of human blood remaining after separation of the cellular elements from blood collected in a container containing an anticoagulant, or separated by continuous filtration or centrifugation of anti-coagulated blood in an apheresis procedure; it is intended for the manufacture of plasma derived medicinal products, in particular albumin, coagulation factors and immunoglobulins of human origin and specified in the European Pharmacopoeia (Ph. Eur.) monograph "Human Plasma for fractionation" (0853).

Plasma Master File (PMF)

A Plasma Master File, as referred to in the Order of the Minister of Public Health No. 906/2006, as amended (Part III, No. 1.1.a), is a stand-alone document, which is separate from the dossier for marketing authorisation. It provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipients and active substances, which are part of plasma, derived medicinal products or medical devices.

Processing

According to the terminology of the Order of the Minister of Public Health No. 1132/2007, "processing means any step in the preparation of blood component that is carried out between the collection of blood and the issuing of a blood component", e.g. separation and freezing of blood components. In this Annex, processing in addition refers to those operations performed at the blood establishment that are specific to plasma to be used for fractionation.

Qualified Person (QP)

The qualified person is the person referred to in Law No. 95/2006, Title XVII (Art. 757).

Responsible Person (RP)

The responsible person is the person referred to in Law No. 282/2005 (Art. 19).

Third countries contract fractionation program

This is a contract fractionation in a plant of a fractionator/manufacturer in the EU/EEA, using starting material from third countries and manufacturing products not intended for the EU/EEA market.

1. Scope

The provisions of this Annex apply to medicinal products derived from human blood or plasma, fractionated in or imported into the EU/EEA. The Annex applies also to the starting material (e.g. human plasma) for these products. In line with the conditions set out in Law No. 95/2006 and in the Order of the Minister of Public Health No. 906/2006, as amended, the requirements apply also for stable derivatives of human blood or human plasma (e.g. Albumin) incorporated into medical devices.

1.2 This Annex defines specific Good Manufacturing Practices (GMP) requirements for processing, storage and transport of human plasma used for fractionation and for the manufacture of medicinal products derived from human blood or plasma.

1.3 The Annex addresses specific provisions for when starting material is imported from third countries and for contract fractionation programs for third countries.

1.4 The Annex does not apply to blood components intended for transfusion.

2. Principles

2.1. Medicinal products derived from human blood or plasma (and their active substances which are used as starting materials) must comply with the principles and guidelines of Good Manufacturing Practice (as laid down in the Order of the Minister of Public Health No. 906/2006, Part I, No. 3.2.1.1.b). Certain special features arise from the biological nature of the source material. For example, disease transmitting agents, especially viruses, may contaminate the source material. The quality and safety of these products relies therefore on the control of source materials and their origin as well as on the subsequent manufacturing procedures, including infectious marker testing, virus removal and virus inactivation.

2.2 In principle, active substances used as starting material for medicinal products must comply with the principles and guidelines of Good Manufacturing Practice (see 2.1). For starting materials derived from human blood and plasma the requirements for the collection and testing defined in Law No. 282/2005 are to be followed. Collection and testing must be performed in accordance with an appropriate quality system for which standards and specifications are defined in the Annex to the Order of the Minister of Public Health No. 1132/2007 and interpreted in the Good Practice guidelines referred to in this Order. Furthermore, the requirements of the Order of the Minister of Public Health No. 1228/2006 on traceability and serious adverse reactions and serious adverse event notifications from the donor to the recipient apply. In addition the monographs of the European Pharmacopoeia are to be observed (The Order of the Minister of Public Health No. 906/2006, Part III No. 1.1.b).

2.3 Starting materials for the manufacture of medicinal products derived from human blood or plasma imported from third countries and intended for use or distribution in the EU/EEA must meet standards which are equivalent to Community Standards and specifications relating to a quality system for blood establishments as set out in Order of the Minister of Public Health No. 1228/2006, the traceability and serious adverse reaction and serious adverse event notification requirements as set out in Order of the Minister of Public Health No. 1228/2006 and the technical requirements for blood and blood components as set out in Commission Directive 2004/33/EC (Recital 4; point 2.3 of Annex V)

2.4 In the case of third country contract fractionation programs the starting material imported from third countries must be in compliance with the quality and safety requirements as laid down in Directive 2002/98/EC and in Annex V of Directive 2004/33/EC. The activities conducted within the EU/EEA must fully comply with GMP. Consideration should be given to the Community standards and specifications relating to a quality system for blood establishments set out in Order of the Minister of Public Health No. 1132/2007, the traceability requirements and notification of serious adverse reactions and events set out in Order of the Minister of Public Health No. 1228/2006 and the relevant WHO guidelines and recommendations as listed in the Annex.

2.5 For all subsequent steps after collection and testing (e.g. processing (including separation), freezing, storage and transport to the manufacturer) the requirements of Law No. 95/2006, Title XVII apply and must therefore be done in accordance with the principles and guidelines of Good Manufacturing Practice. Normally, these activities would be carried out under the responsibility of a Qualified Person in an establishment with a manufacturing authorisation. Where specific processing steps in relation to plasma for fractionation take place in a blood establishment, the specific appointment of a Qualified Person may, however, not be proportionate given the presence and responsibility of a Responsible Person. To address this particular situation and to ensure the legal responsibilities of the Qualified Person are properly addressed, the

fractionation plant/manufacturer should establish a contract in accordance with Chapter 7 of the GMP Guide with the blood establishment that defines respective responsibilities and the detailed requirements in order to ensure compliance. The Responsible Person of the blood establishment and the Qualified Person of the fractionation/manufacturing plant (see 3.5) should be involved in drawing up this contract. The Qualified Person should ensure that audits are performed to confirm that the blood establishment complies with the contract.

2.6 Specific requirements for documentation and other arrangements relating to the starting materials of plasma-derived medicinal products are defined in the Plasma Master File.

3. Quality Management

3.1 Quality management should govern all stages from donor selection to delivery of the finished product. Reference is made to the Order of the Minister of Public Health No. 1228/2006 for traceability up to and including the delivery of plasma to the fractionation plant, and to the Order of the Minister of Public Health No. 1132/2007 for all stages concerning collection and testing of human blood and human plasma to be used for the manufacture of medicinal products.

3.2 Blood or plasma used as source material for the manufacture of medicinal products must be collected by blood establishments and be tested in laboratories which apply quality systems in accordance with the Order of the Minister of Public Health No. 1132/2007, are authorised by a national competent authority and are subject to regular inspections as referred to in Law No. 282/2005. Third country contract fractionation programs have to be notified to the competent EU authority by the manufacturer as referred to in Law No. 95/2006, Title XVII.

3.3 If plasma is imported from third countries it should only be purchased from approved suppliers (e.g. blood establishments, including external warehouses). They should be named in the specifications for starting materials as defined by the fractionation plant/manufacturer, and be accepted by an EU/EEA competent authority (e.g. following an inspection) and by the Qualified Person of the fractionation plant in the EU/EEA. Certification and release of plasma (plasma for fractionation) as starting material is mentioned in section 6.8.

3.4 Supplier qualification, including audits, should be performed by the fractionation plant/manufacturer of the finished product according to written procedures. Re-qualification of suppliers should be performed at regular intervals taking a risk-based approach into account.

3.5 The fractionation plant/manufacturer of the finished product should establish written contracts with the supplying blood establishments. As a minimum the following key aspects should be addressed:

- definition of duties and respective responsibilities
- quality system and documentation requirements
- donor selection criteria and testing
- requirements for the separation of blood into blood components/plasma
- freezing of plasma;
- storage and transport of plasma;

The test results of all units supplied by the blood establishment should be available to the fractionation plant/manufacturer of the medicinal product. In addition, any fractionation step subcontracted should be defined in a written contract.

3.6 A formal change control system should be in place to plan, evaluate and document all changes that may affect the quality or safety of the products, or traceability. The potential impact of proposed changes should be evaluated. The need for additional

testing and validation, especially viral inactivation and removal steps, should be determined.

3.7 An adequate safety strategy should be in place to minimise the risk from infectious agents and emerging infectious agents. This strategy should involve a risk assessment that:

- defines an inventory holding time (internal quarantine time) before processing the plasma i.e. to remove former units [12];
- considers all aspects of virus reduction and/or testing for infectious agents or surrogates;
- considers the virus reduction capabilities, the pool size and other relevant aspects of the manufacturing processes.

4. Traceability and post-collection measures

4.1 There must be a system in place that enables each donation to be traced, from the donor and the donation via the blood establishment through to the batch of medicinal product and vice versa.

4.2 Responsibilities for traceability of the product should be defined (there should be no gaps):

- from the donor and the donation in the blood establishment to the fractionation plant (this is the responsibility of the RP at the blood establishment),
- from the fractionation plant to the manufacturer of the medicinal product and any secondary facility, whether a manufacturer of a medicinal product or of a medical device (this is the responsibility of the QP).

4.3 Data needed for full traceability must be stored for at least 30 years, according to Article 12 of the Order of the Minister of Public Health No. 1228/2006 and Article 37 of Law No. 282/2005.[13]

4.4 The contracts (as mentioned in 3.5) between the blood establishments (including testing laboratories) and the fractionation plant/manufacturer should ensure that traceability and post collection measures cover the complete chain from the collection of the plasma to all manufacturers responsible for release of the finished products.

4.5 The blood establishments should notify the fractionating plant/manufacturer of any event which may affect the quality or safety of the product including events listed in Annex 2 part A and Annex 3 part A of the Norms of the Order of the Minister of Public Health No. 1228/2006, and other relevant information found subsequent to donor acceptance or release of the plasma, e.g. look back information [14] (post-collection information). Where the fractionation plant/manufacturer is located in a third country, the information should be forwarded to the manufacturer responsible for release in the EU/EEA of any product manufactured from the plasma concerned. In both cases, if relevant for the quality or safety of the final product, this information should be forwarded to the competent authority[15] responsible for the fractionation plant/manufacturer.

4.6 The notification procedure as described in Section 4.5 also applies when an inspection of a blood establishment by a competent authority leads to a withdrawal of an existing authorisation/certificate/approval.

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[12] Plasma units donated by donors during a defined period (as defined on a national/EU basis) before it is found that a donation from a high-risk donor should have been excluded from processing, e.g. due to a positive test result

[13] Both Directives are linked to Article 821 of Law No. 95/2006, Title XVII by defining specific rules for medicinal products derived from human blood or plasma.

[14] Information that appears if a subsequent donation from a donor previously found negative for viral markers is found positive for any of the viral markers or any other risk factors which may induce a viral infection

[15] As referred to in Law No. 95/2006, Title XVII

4.7 The management of post-collection information should be described in standard operating procedures and taking into account obligations and procedures for informing the competent authorities. Post-collection measures should be available as defined in the "Note for Guidance on Plasma Derived Medicinal Products" in its current version as adopted by the Committee for Medicinal Products for Human Use (CHMP) and published by the European Medicines Agency[16].

5. Premises and equipment

5.1 In order to minimise microbiological contamination or the introduction of foreign material into the plasma pool, thawing and pooling of plasma units should be performed in an area conforming at least to the Grade D requirements defined in Annex 1 of the GMP Guideline. Appropriate clothing should be worn including face masks and gloves. All other open manipulations during the manufacturing process should be done under conditions conforming to the appropriate requirements of Annex 1 of the GMP Guideline.

5.2 Environmental monitoring should be performed regularly, especially during the 'opening' of plasma containers, and during subsequent thawing and pooling processes in accordance with Annex 1 of the EU-GMP Guide. Acceptance limits should be specified.

5.3 In the production of plasma-derived medicinal products, appropriate viral inactivation or removal procedures are used and steps should be taken to prevent cross contamination of treated with untreated products. Dedicated and distinct premises and equipment should be used for manufacturing steps after viral inactivation treatment.

5.4 To avoid placing routine manufacture at risk of contamination from viruses used during validation studies, the validation of methods for virus reduction should not be conducted in production facilities. Validation should be performed according to the "Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies validating the Inactivation and Removal of Viruses" in its current version as adopted by the Committee for Medicinal Products for Human Use (CHMP) and published by the European Medicines Agency[17].

6. Manufacturing

Starting material

6.1 The starting material should comply with the requirements of all relevant monographs of the European Pharmacopoeia and of the conditions laid down in the respective marketing authorisation dossier including the Plasma Master File. These requirements should be defined in the written contract (see 3.5) between the blood establishment and the fractionating plant/manufacturer and controlled through the quality system.

6.2 The starting material for third country contract fractionation programs should comply with the requirements as specified in 2.4.

6.3 Depending on the type of collection (i.e. either whole blood collection or automated apheresis) different processing steps may be required. All processing steps (e.g. centrifugation and/or separation, sampling, labelling, freezing) should be defined in written procedures.

6.4 Any mix-ups of units and of samples, especially during labelling, as well as any contamination, e.g. when cutting the tube segments/sealing the containers, must be avoided.

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[16] Current version at date of publication: CPMP/BWP/269/95

[17] Current version at date of publication: CHMP/BWP/268/95

6.5 Freezing is a critical step for the recovery of proteins that are labile in plasma, e.g. clotting factors. Freezing should therefore be performed as soon as possible after collection (see the European Pharmacopoeia monograph No. 0853 "*Human Plasma for Fractionation*" and where relevant, monograph No 1646 "*Human Plasma pooled and treated for virus inactivation*"), following a validated method.

6.6 The storage and transport of blood or plasma at any stage in the transport chain to the fractionation plant should be defined and recorded. Any deviation from the defined temperature should be notified to the fractionation plant. Qualified equipment and validated procedures should be used.

Certification/release of plasma for fractionation as starting material

6.7 Plasma for fractionation should only be released, i.e. from a quarantine status, through systems and procedures that assure the quality needed for the manufacture of the finished product. It should only be distributed to the plasma fractionation plant/manufacturer after it has been documented by the Responsible Person (or in case of blood/plasma collection in third countries by a person with equivalent responsibilities and qualifications) that the plasma for fractionation does comply with the requirements and specifications defined in the respective written contracts and that all steps have been performed in accordance with Good Practice and GMP Guidelines, as appropriate.

6.8 On entering the fractionation plant, the plasma units should be released for fractionation under the responsibility of the Qualified Person. The Qualified Person should confirm that the plasma complies with the requirements of all relevant monographs and the conditions laid down in the respective marketing authorisation dossier including the Plasma Master File or, in case of plasma to be used for third country contract fractionation programs, with the requirements as specified in 2.4.

Processing of plasma for fractionation

6.9 The steps used in the fractionation process vary according to product and manufacturer and usually include several fractionation/purification procedures, some of which may contribute to the inactivation and/or removal of potential contamination.

6.10 Requirements for the processes of pooling, pool sampling and fractionation/purification and virus inactivation/removal should be defined and followed thoroughly.

6.11 The methods used in the viral inactivation process should be undertaken with strict adherence to validated procedures and in compliance with the methods used in the virus validation studies. Detailed investigation of failures in virus inactivation procedures should be performed. Adherence to the validated production process is especially important in the virus reduction procedures as any deviation could result in a safety risk for the final product. Procedures taking this risk into consideration should be in place.

6.12 Any reprocessing or reworking may only be performed after a quality risk management exercise has been performed and using processing steps as defined in the relevant marketing authorisation.

6.13 A system for clearly segregating/distinguishing between products or intermediates which have undergone a process of virus reduction, from those which have not, should be in place.

6.14 Depending on the outcome of a thorough risk management process (taking into consideration possible differences in epidemiology) production in campaigns including clear segregation and defined validated cleaning procedures should be adopted when plasma/intermediates of different origins is processed at the same plant. The requirement for such measures should be based on the recommendations of the Guideline on

Epidemiological Data on Blood Transmissible Infections[18]. The risk management process should consider whether it is necessary to use dedicated equipment in the case of third country contract fractionation programs.

6.15 For intermediate products intended to be stored, a shelf-life should be defined based on stability data.

6.16 The storage and transport of intermediate and finished medicinal products at any stage of the transport chain should be specified and recorded. Qualified equipment and validated procedures should be used.

7. Quality control

7.1 Testing requirements for viruses or other infectious agents should be considered in the light of knowledge emerging on infectious agents and on the availability of appropriate, validated test methods.

7.2 The first homogeneous plasma pool (e.g. after separation of the cryoprecipitate from the plasma pool) should be tested using validated test methods of suitable sensitivity and specificity, according to the relevant European Pharmacopoeia monographs (e.g. No. 0853).

8. Release of intermediate and finished products

8.1 Only batches derived from plasma pools tested and found negative for virus markers/ antibodies and found in compliance with the relevant European Pharmacopoeia monographs, including any specific virus cut-off limits, and with the approved specifications (e.g. Plasma Master File), should be released.

8.2 The release of intermediates intended for further in-house processing or delivery to a different site, and, the release of finished products should be performed by the Qualified Person and in accordance with the approved marketing authorisation.

8.3 The release of intermediates and finished products used in third country contract fractionation programs should be performed by the Qualified Person on the basis of standards agreed with the contract giver, and compliance with EU GMP standards. Compliance with relevant European Pharmacopoeia monographs may not be applicable, as these products are not intended for the use on the European market.

9. Retention of plasma pool samples

One plasma pool may be used to manufacture more than one batch and/or product. Retention samples and corresponding records from every pool should be kept for at least one year after the expiry date of the finished medicinal product with the longest shelf-life derived from the pool.

10. Disposal of waste

There should be written procedures for the safe and documented storage and disposal of waste, disposable and rejected items (e.g. contaminated units, units from infected donors, out of date blood, plasma, intermediate or finished products).

[18] EMEA/CPMP/BWP/125/04

Annex

A) Romania has implemented the following Laws and Orders:

1. for collection and testing of blood and blood components:

Law/Order	Title	Scope
Law No. 282/2005	on the organisation of the activity consisting of blood transfusion, donation of human blood and blood components, as well as the insurance of quality and health security, in view of their therapeutic use.	**Art. 3** (1) This Law applies to the collection, biologic control, processing, storage, distribution and administration of human blood and blood components.
Commission Directive 2004/33/EC	Implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components	Defines the provision of information to prospective donors and information required from donors (Part A and B, Annex II), eligibility of donors (Annex III), storage, transport and distribution conditions for blood and blood components (Annex IV), as well as quality and safety requirements for blood and blood components (Annex V).
Order of the Minister of Public Health No. 1228/2006	on approval of the Norms on the organisation of the haemovigilance system, traceability insurance and of the Regulation on the recording and reporting system in case incidents and severe adverse reactions occur, related to the collection and administration of human blood and blood components	Defines the requirements for traceability for blood centres, donors, blood and blood components and for the final purpose of each unit, regardless of the proposed goal. Moreover, it defines the requirements concerning the report of incidents and severe adverse reactions.
	on approval of the Norms on the standards and specifications related to the quality system for medical institutions which conduct various activities in the field of blood transfusions.	Defines the enforcement of the quality standards and specifications referred to in Art. 756 of Law No. 95/2006, Title XVII – The medicinal product.

2. for collection and regulatory submission of data/information for plasma for fractionation:

Law/Order	Title	Scope
Law No. 95/2006 Title XVII –The medicinal product	The medicinal product	Art. 696 (1) The provisions of this title apply to medicinal products for human use, meant for marketing, manufactured industrially or manufactured by an industrial process.

Order of the Minister of Public Health No. 906/2006	on approval of the Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products	
Order of the Minister of Public Health No. 905/2006	on approval of the Principles and guidelines for good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use	on approval of the Principles and guidelines for good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
Guideline on the Good Manufacturing Practice	Interpretation of the Principles and guidelines for Good Manufacturing Practice	
EMEA/CHMP/BWP/3794/03 Rev.1, 15. Nov. 2006	Guideline on the scientific data requirements for a plasma master file (PMF Revision 1)	
EMEA/CHMP/BWP/548524/2008 EMEA Guideline	Guideline on epidemiological data on blood transmissible infections	

B). Other relevant documents:

Document	Title	Scope
Recommendation No. R (95) 15 (Council of Europe)	Guide to the Preparation, use and quality assurance of blood components	
Order of the Minister of Health Recommendations for the production, control and regulation of human plasma for fractionation. Annex 4 in: WHO Expert Committee on Biological Standardization. Fifty-sixth report. Geneva, World Health Organization, 2007 (WHO Technical Report Series, No. 941)	WHO Recommendations for the production, control and regulation of human plasma for fractionation	Guidance on the production, control and regulation of human plasma for fractionation
WHO guidelines on Good Manufacturing Practices for blood establishments		

Reference should be made to the latest versions of these documents for current guidance.

ANNEX 15

QUALIFICATION AND VALIDATION

Principle

1. This Annex describes the principles of qualification and validation which are applicable to the manufacture of medicinal products. It is a requirement of GMP that manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations. Significant changes to the facilities, the equipment and the

processes, which may affect the quality of the product, should be validated. A risk assessment approach should be used to determine the scope and extent of validation.

Planning for validation

2. All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents.
3. The VMP should be a summary document which is brief, concise and clear.
4. The VMP should contain data on at least the following:
   a) Validation policy;
   b) Organisational structure of validation activities;
   c) Summary of facilities, systems, equipment and processes to be validated;
   d) Documentation format: the format to be used for protocols and reports;
   e) Planning and scheduling;
   f) Change control;
   g) Reference to existing documents.

5. In case of large projects, it may be necessary to create separate validation master plans.

Documentation

6. A written protocol should be established that specifies how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify critical steps and acceptance criteria.
7. A report that cross-references the qualification and/or validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification.
8. After completion of a satisfactory qualification, a formal release for the next step in qualification and validation should be made as a written authorisation.

Qualification

Design qualification

9. The first element of the validation of new facilities, systems or equipment could be design qualification (DQ).
10. The compliance of the design with GMP should be demonstrated and documented.

Installation qualification

11. Installation qualification (IQ) should be performed on new or modified facilities, systems and equipment.
12. IQ should include, but not be limited to the following:
    a) installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;
    b) collection and collation of supplier operating and working instructions and maintenance requirements;
    c) calibration requirements;
    d) verification of materials of construction.

Operational qualification

13. Operational qualification (OQ) should follow Installation qualification.

14. OQ should include, but not be limited to the following:

a) tests that have been developed from knowledge of processes, systems and equipment;

b) tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as “worst case” conditions.

15. The completion of a successful Operational qualification should allow the finalisation of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements.

It should permit a formal "release" of the facilities, systems and equipment.

Performance qualification

16. Performance qualification (PQ) should follow successful completion of Installation qualification and Operational qualification.
17. PQ should include, but not be limited to the following:
    a) tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment;
    b) tests to include a condition or set of conditions encompassing upper and lower operating limits.
18. Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ.

Qualification of established (in-use) facilities, systems and equipment

19. Evidence should be available to support and verify the operating parameters and limits for the critical variables of the operating equipment. Additionally, the calibration, cleaning, preventative maintenance, operating procedures and operator training procedures and records should be documented.

Process validation

General

20. The requirements and principles outlined in this chapter are applicable to the manufacture of pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes and re-validation.
21. Process validation should normally be completed prior to the distribution and sale of the medicinal product (prospective validation). In exceptional circumstances, where this is not possible, it may be necessary to validate processes during routine production (concurrent validation). Processes in use for some time should also be validated (retrospective validation).
22. Facilities, systems and equipment to be used should be qualified and analytical testing methods should be validated. Staff taking part in the validation work should be appropriately trained.
23. Facilities, systems, equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner.

Prospective validation

24. Prospective validation should include, but not be limited to the following:
    a) short description of the process;
    b) summary of the critical processing steps to be investigated;
    c) list of the equipment/facilities to be used (including measuring/ monitoring/recording equipment) together with its calibration status
    d) finished product specifications for release;

e) list of analytical methods, as appropriate;
f) proposed in-process controls with acceptance criteria;
g) additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;
h) sampling plan;
i) methods for recording and evaluating results;
j) functions and responsibilities;
k) proposed timetable.

25. Using this defined process (including specified components) a series of batches of the final product may be produced under routine conditions. In theory the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, would constitute a validation of the process.
26. Batches made for process validation should be the same size as the intended industrial scale batches.
27. If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise, and with the marketing authorisation.

Concurrent validation

28. In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.
29. The decision to carry out concurrent validation must be justified, documented and approved by authorised personnel.
30. Documentation requirements for concurrent validation are the same as specified for prospective validation.

Retrospective validation

31. Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.
32. Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.
33. The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance log books, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results.
34. 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. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.
35. For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches may be examined if justified.

Cleaning validation

36. Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure. The rationale for selecting limits of carry over of product residues, cleaning agents and microbial contamination should be logically based on the materials involved. The limits should be achievable and verifiable.
37. 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.
38. Normally only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to noncontact parts. The intervals between use and cleaning as well as cleaning and reuse should be validated. Cleaning intervals and methods should be determined.
39. For cleaning procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilising a “worst case” approach can be carried out which takes account of the critical issues.
40. Typically three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.
41. "Test until clean" is not considered an appropriate alternative to cleaning validation.
42. Products which simulate the physicochemical properties of the substances to be removed may exceptionally be used instead of the substances themselves, where such substances are either toxic or hazardous.

Change control

43. Written procedures should be in place to describe the actions to be taken if a change is proposed to a starting material, product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or reproducibility of the process. Change control procedures should ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specifications.
44. All changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. The need for, and the extent of, requalification and re-validation should be determined.

Revalidation

45. Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation.

GLOSSARY

Definitions of terms relating to qualification and validation which are not given in the glossary of the current GMP Guideline, but which are used in this Annex, are given below.

Change control

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state.

Cleaning validation

Cleaning validation is documented evidence that an approved cleaning procedure will provide equipment which is suitable for processing medicinal products.

Concurrent validation

Validation carried out during routine production of products intended for sale.

Installation qualification (IQ)

The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.

Operational qualification (OQ)

The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.

Performance qualification (PQ)

The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification.

Process validation

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

Prospective validation

Validation carried out before routine production of products intended for sale.

Retrospective validation

Validation of a process for a product which has already been marketed based upon accumulated manufacturing, testing and control batch data.

Revalidation

A repeat of the process validation to provide an assurance that changes in the process/ equipment introduced in accordance with change control procedures do not adversely affect process characteristics and product quality.

Risk analysis

Method to assess and characterise the critical parameters in the functionality of an equipment or process.

Simulated product

A material that closely approximates the physical and, where practical, the chemical characteristics (e.g. viscosity, particle size, pH etc.) of the product under validation. In many cases, these characteristics may be satisfied by a placebo product batch.

„Worst case"

A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

ANNEX 16

CERTIFICATION BY A QUALIFIED PERSON AND BATCH RELEASE

1. Scope

1.1. This Annex to the Guideline on the Good Manufacturing Practice for Medicinal Products provides guidance on the certification by a Qualified Person (Q.P.) and batch release within the European Community (EC) or European Economic Area (EEA) of medicinal products holding a marketing authorisation or made for export. The relevant legislative requirements are contained in Article 760 of Law No. 95/2006 on the healthcare reform, Title XVII – The medicinal product.

1.2. This Annex covers in particular those cases where a batch has had different stages of production or testing conducted at different locations or by different manufacturers, and where an intermediate or bulk production batch is divided into more than one finished product batch. It also covers the release of batches which have been imported to the EC/EEA both when there is and is not a mutual recognition agreement between the Community and the third country. This guideline may also be applied to investigational medicinal products, subject to any difference in the legal provisions and more specific guidance in Annex 13 to this Guideline.

1.3. This Annex does not, of course, describe all possible arrangements which are legally acceptable. Neither does it address the official control authority batch release which may be specified for certain blood and immunological products in accordance with Article 821 and 822 of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product.

1.4. The basic arrangements for batch release for a product are defined by its Marketing Authorisation. Nothing in this Annex should be taken as overriding those arrangements.

2. Principle

2.1. Each batch of finished product must be certified by a Q.P. within the EC/EEA before being released for sale or supply in the EC/EEA or for export.

2.2. The scope of controlling batch release in this manner is:
- to ensure that the batch has been manufactured and checked in accordance with the requirements of its marketing authorisation, the principles and guidelines of the Romanian Good Manufacturing Practice or the Good Manufacturing Practice of a third country recognised as equivalent under a mutual recognition agreement and any other relevant legal requirement before it is placed on the market, and

- in the event that a defect needs to be investigated or a batch recalled, to ensure that the Q.P. who certified the batch and the relevant records are readily identifiable.

3. Introduction

3.1 Manufacture, including quality control testing, of a batch of medicinal products takes place in stages which may be conducted at different sites and by different manufacturers. Each stage should be conducted in accordance with the relevant marketing authorisation, Good Manufacturing Practice and the laws of the Member State concerned and should be taken into account by the Q.P. who certifies the finished product batch before release to the market.

3.2 However in an industrial situation it is usually not possible for a single Q.P. to be closely involved with every stage of manufacture. The Q.P. who certifies a finished product batch may need therefore to rely in part on the advice and decisions of others. Before doing so he should ensure that this reliance is well founded, either from personal knowledge or from the confirmation by other Q.P.s within a quality system which he has accepted.

3.3 When some stages of manufacture occur in a third country it is still a requirement that production and testing are in accordance with the marketing authorisation, that the manufacturer is authorised according to the laws of the country concerned and that manufacture follows good manufacturing practices at least equivalent to those of the EC.

3.4 Certain words used in this Annex have particular meanings attributed to them, as defined in the Glossary.

4. General

4.1 One batch of finished product may have different stages of manufacture, importation, testing and storage before release conducted at different sites. Each site should be approved under one or more manufacturing authorisations and should have at its disposal the services of at least one Q.P. However the correct manufacture of a particular batch of product, regardless of how many sites are involved, should be the overall concern of the Q.P. who certifies that finished product batch before release.

4.2 Different batches of a product may be manufactured or imported and released at different sites in the EC/EEA. For example a Community marketing authorisation may name batch release sites in more than one member state, and a national authorisation may also name more than one release site. In this situation the Marketing Authorisation Holder and each site authorised to release batches of the product should be able to identify the site at which any particular batch has been released and the Q.P. who was responsible for certifying that batch.

4.3 The Q.P. who certifies a finished product batch before release may do so based on his personal knowledge of all the facilities and procedures employed, the expertise of the persons concerned and of the quality system within which they operate. Alternatively he may rely on the confirmation by one or more other Q.P.s of the compliance of intermediate stages of manufacture within a quality system which he has accepted.
This confirmation by other Q.P.s should be documented and should identify clearly the matters which have been confirmed. The systematic arrangements to achieve this should be defined in a written agreement.

4.4 The agreement mentioned above is required whenever a Q.P. wishes to rely on the confirmation by another Q.P. The agreement should be in general accordance with Chapter 7 of this Guideline. The Q.P. who certifies the finished product batch should ensure the arrangements in the agreement are verified. The form of such an agreement should be appropriate to the relationship between the parties; for example a standard

operating procedure within a company or a formal contract between different companies even if within the same group.

4.5 The agreement should include an obligation on the part of the provider of a bulk or intermediate product to notify the recipient(s) of any deviations, out-of-specification results, non-compliance with GMP, investigations, complaints or other matters which should be taken into account by the Q.P. who is responsible for certifying the finished product batch.

4.6 When a computerised system is used for recording certification and batch release, particular note should be taken of the guidance in Annex 11 to this Guideline.

4.7 Certification of a finished product batch against a relevant marketing authorisation by a Q.P. in the EC/EEA need not be repeated on the same batch provided the batch has remained within the EC/EEA.

4.8 Whatever particular arrangements are made for certification and release of batches, it should always be possible to identify and recall without delay all products which could be rendered hazardous by a quality defect in the batch.

5. Batch testing and release of medicinal products manufactured in EC/EEA

5.1 When all manufacture occurs at a single authorised site

When all production and control stages are carried out at a single site, the conduct of certain checks and controls may be delegated to others but the Q.P. at this site who certifies the finished product batch normally retains personal responsibility for these within a defined quality system. However he may, alternatively, take account of the confirmation of the intermediate stages by other Q.Ps on the site who are responsible for those stages.

*5.2 Different stages of manufacture are conducted at different sites within the same company*When different stages of the manufacture of a batch are carried out at different sites within the same company (which may or may not be covered by the same manufacturing authorisation) a Q.P. should be responsible for each stage. Certification of the finished product batch should be performed by a Q.P. of the manufacturing authorisation holder responsible for releasing the batch to the market, who may take personal responsibility for all stages or may take account of the confirmation of the earlier stages by the relevant Q.P.s responsible for those stages.

5.3 Some intermediate stages of manufacture are contracted to a different company.

One or more intermediate production and control stages may be contracted to a holder of a manufacturing authorisation in another company. A Q.P. of the contract giver may take account of the confirmation of the relevant stage by a Q.P. of the contract acceptor but is responsible for ensuring that this work is conducted within the terms of a written agreement. The finished product batch should be certified by a Q.P. of the manufacturing authorisation holder responsible for releasing the batch to the market.

5.4 *A bulk production batch is assembled at different sites into several finished product batches which are released under a single marketing authorisation. This could occur, for example, under a national marketing authorisation when the assembly sites are all within one member state or under a Community marketing authorisation when the sites are in more than one member state.*

5.4.1 One alternative is for a Q.P. of the manufacturing authorisation holder making the bulk production batch to certify all the finished product batches before release to the market. In doing so he may either take personal responsibility for all manufacturing stages or take account of the confirmation of assembly by the Q.P.s of the assembly sites.

5.4.2 Another alternative is for the certification of each finished product batch before release to the market to be performed by a Q.P of the manufacturer who has conducted the final

assembly operation. In doing so he may either take personal responsibility for all manufacturing stages or take account of the confirmation of the bulk production batch by a Q.P. of the manufacturer of the bulk batch.

5.4.3 In all cases of assembly at different sites under a single marketing authorisation, there should be one person, normally a Q.P. of themanufacturer of the bulk production batch, who has an overall responsibility for all released finished product batches which are derived from one bulk production batch. The duty of this person is to be aware of any quality problems reported on any of the finished product batches and to co-ordinate any necessary action arising from a problem with the bulk batch.

While the batch numbers of the bulk and finished product batches are not necessarily the same, there should be a documented link between the two numbers so that an audit trail can be established.

5.5 *A bulk production batch is assembled at different sites into several finished product batches which are released under different marketing authorisations. This could occur, for example, when a multi-national organisation holds national marketing authorisations for a product in several member states or when a generic manufacturer purchases bulk products and assembles and releases them for sale under his own marketing authorisation.*

5.5.1 A Q.P. of the manufacturer doing the assembly who certifies the finished product batch may either take personal responsibility for all manufacturing stages or may take account of the confirmation of the bulk production batch by a Q.P. of the bulk product manufacturer.

5.5.2 Any problem identified in any of the finished product batches which may have arisen in the bulk production batch should be communicated to the Q.P. responsible for confirming the bulk production batch, who should then take any necessary action in respect of all finished product batches produced from the suspected bulk production batch. This arrangement should be defined in a written agreement.

5.6 *A finished product batch is purchased and released to the market by a manufacturing authorisation holder in accordance with his own marketing authorisation. This could occur, for example, when a company supplying generic products holds a marketing authorisation for products made by another company, purchases finished products which have not been certified against his marketing authorisation and releases them under his own manufacturing authorisation in accordance with his own marketing authorisation.*

In this situation a Q.P. of the purchaser should certify the finished product batch before release. In doing so he may either take personal responsibility for all manufacturing stages or may take account of the confirmation of the batch by a Q.P. of the vendor manufacturer.

5.7 The quality control laboratory and the production site are authorised under different manufacturing authorisations.

A Q.P. certifying a finished product batch may either take personal responsibility for the laboratory testing or may take account of the confirmation by another Q.P. of the testing and results. The other laboratory and Q.P. need not be in the same member state as the manufacturing authorisation holder releasing the batch. In the absence of such confirmation the Q.P. should himself have personal knowledge of the laboratory and its procedures relevant to the finished product to be certified.

6. Batch testing and release of products imported from a thirs country

6.1 *General*

6.1.1 Importation of finished products should be conducted by an importer as defined in the glossary to this Annex.

6.1.2 Each batch of imported finished product should be certified by a Q.P. of the importer before release for sale in the EC/EEA.

6.1.3 Unless a mutual recognition agreement is in operation between the Community and the third country (see Section 7), samples from each batch should be tested in the EC/EEA before certification of the finished product batch by a Q.P. Importation and testing need not necessarily be performed in the same member state.

6.1.4 The guidance in this section should also be applied as appropriate to the importation of partially manufactured products.

6.2 *A complete batch or the first part of a batch of a medicinal product is imported*

The batch or part batch should be certified by a Q.P of the importer before release. This Q.P. may take account of the confirmation of the checking, sampling or testing of the imported batch by a Q.P. of another manufacturing authorisation holder (i.e. within EC/EEA).

6.3 Part of a finished product batch is imported after another part of the same batch has previously been imported to the same or a different site.

6.3.1 A Q.P. of the importer receiving a subsequent part of the batch may take account of the testing and certification by a Q.P. of the first part of the batch. If this is done, the Q.P. should ensure, based on evidence, that the two parts do indeed come from the same batch, that the subsequent part has been transported under the same conditions as the first part and that the samples that were tested are representative of the whole batch.

6.3.2 The conditions in paragraph 6.3.1 is most likely to be met when the manufacturer in the third country and the importer(s) in the EC/EEA belong to the same organisation operating under a corporate system of quality assurance. If the Q.P. cannot ensure that the conditions in paragraph 6.3.1 are met, each part of the batch should be treated as a separate batch.

6.3.3 When different parts of the batch are released under the same marketing authorisation, one person, normally a Q.P. of the importer of the first part of a batch, should take overall responsibility for ensuring that records are kept of the importation of all parts of the batch and that the distribution of all parts of the batch is traceable within the EC/EEA. He should be made aware of any quality problems reported on any part of the batch and should co-ordinate any necessary action concerning these problems and their resolution.

This should be ensured by a written agreement between all the importers concerned.

6.4 Location for sampling for testing in EC/EEA.

6.4.1 Samples should be representative of the batch and be tested in the EC/EEA. In order to represent the batch it may be preferable to take some samples during processing in the third country. For example, samples for sterility testing may best be taken throughout the filling operation. However in order to represent the batch after storage and transportation some samples should also be taken after receipt of the batch in the EC/EEA.

6.4.2 When any samples are taken in a third country, they should either be shipped with and under the same conditions as the batch which they represent, or if sent separately it should be demonstrated that the samples are still representative of the batch, for example by defining and monitoring the conditions of storage and

shipment. When the Q.P. wishes to rely on testing of samples taken in a third country, this should be justified on technical grounds**.**

7. Batch testing and release of products imported from a third country with which the EC has a mutual recognition agreement (MRA)

7.1 Unless otherwise specified in the agreement, an MRA does not remove the requirement for a Q.P. within the EC/EEA to certify a batch before it is released for sale or supply within the EC/EEA. However, subject to details of the particular agreement, the Q.P. of the importer may rely on the manufacturer's confirmation that the batch has been made and tested in accordance with its marketing authorisation and the GMP of the third country. and need not repeat the full testing. The Q.P. may certify the batch for release when he is satisfied with this confirmation and that the batch has been transported under the required conditions and has been received and stored in the EC/EEA by an importer as defined in section 8.

7.2 Other procedures**,** including those for receipt and certification of part batches at different times and/or at different sites, should be the same as in Section 6.

8. Routine duties of a Qualified Person

8.1 Before certifying a batch prior to release the Q.P. doing so should ensure, with reference to the guidance above, that at least the following requirements have been met:

a. the batch and its manufacture comply with the provisions of the marketing
authorisation (including the authorisation required for importation where relevant);

b. manufacture has been carried out in accordance with Good Manufacturing
Practice or, in the case of a batch imported from a third country, in accordance with good manufacturing practice standards at least equivalent to EC GMP;

c. the principal manufacturing and testing processes have been validated; account has been taken of the actual production conditions and manufacturing records;

d. any deviations or planned changes in production or quality control have been authorised by the persons responsible in accordance with a defined system. Any changes requiring variation to the marketing or manufacturing authorisation have been notified to and authorised by the relevant authority;

e. all the necessary checks and tests have been performed, including any additional sampling, inspection, tests or checks initiated because of deviations or planned changes;

f. all necessary production and quality control documentation has been completed and endorsed by the staff authorised to do so;

g. all audits have been carried out as required by the quality assurance system;

h. the QP should in addition take into account any other factors of which he is aware which are relevant to the quality of the batch.

A Q.P. may have additional duties in accordance with national legislation or administrative procedures.

8.2 A Q.P. who confirms the compliance of an intermediate stage of manufacture, as described in paragraph 4.3, has the same obligations as above in relation to that stage unless specified otherwise in the agreement between the Q.P.s.

8.3 A Q.P. should maintain his knowledge and experience up to date in the light of technical and scientific progress and changes in quality management relevant to the products which he is required to certify.

8.4 If a Q.P. is called upon to certify a batch of a product type with which he is unfamiliar, for example because the manufacturer for whom he works introduces a new product range or because he starts to work for a different manufacturer, he should first ensure that he has gained the relevant knowledge and experience necessary to fulfil this duty.

9. Glossary

Certain words and phrases in this Annex are used with the particular meanings defined below. Reference should also be made to the Glossary in the main part of the Guide.

Mutual Recognition Agreement (MRA)

The 'appropriate arrangement' between the EC and an exporting third country mentioned in Article 760 (2) of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product.

Certification of the finished product batch

The certification in a register or equivalent document by a Q.P., as defined in Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product, before a batch is released for sale or distribution.

Confirmation

A signed statement that a process or test has been conducted in accordance with GMP and the relevant marketing authorisation, as agreed in writing with the Q.P. responsible for certifying the finished product batch before release.

Importer

The holder of the authorisation required by Article 748 (3) of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product for importing medicinal products from third countries.

Qualified Person (QP)

The person defined in Art. 757 of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product.

Finished product batch

See the definition in the Glossary of the GMP Guideline. In the context of this annex the term in particular denotes the batch of product in its final pack for release to the market.

Bulk production batch

A product batch, of a size described in the application for a marketing authorisation, either ready for assembly into final containers or in individual containers ready for assembly to final packs. (A bulk production batch may, for example, consist of a bulk quantity of liquid product, of solid dosage forms such as tablets or capsules, or of filled ampoules).

ANNEX 17

PARAMETRIC RELEASE

1. Principle

1.1 The definition of Parametric Release used in this Annex is based on that proposed by the European Organisation for Quality: "A system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing process and on the compliance with specific GMP requirements related to Parametric Release."

1.2 Parametric release should comply with the basic requirements of GMP, with applicable annexes and the following guidelines.

2. Parametric release

2.1 It is recognised that a comprehensive set of in-process tests and controls may provide greater assurance of the finished product meeting specification than finished product testing.

2.2 Parametric release may be authorised for certain specific parameters as an alternative to routine testing of finished products. Authorisation for parametric release should be given, refused or withdrawn jointly by those responsible for assessing products together with the GMP inspectors.

3. Parametric release for sterile products

3.1 This section is only concerned with that part of Parametric Release which deals with the routine release of finished products without carrying out a sterility test. Elimination of the sterility test is only valid on the basis of successful demonstration that predetermined, validated sterilising conditions have been achieved.

3.2 A sterility test only provides an opportunity to detect a major failure of the sterility assurance system due to statistical limitations of the method.

3.3 Parametric Release can be authorised if the data demonstrating correct processing of the batch provides sufficient assurance, on its own, that the process designed and validated to ensure the sterility of the product has been delivered.

3.4. At present Parametric release can only be approved for products terminally sterilized in their final container.

3.5 Sterilization methods according to European Pharmacopoeia requirements using steam, dry heat and ionising radiation may be considered for parametric release.

3.6 It is unlikely that a completely new product would be considered as suitable for Parametric Release because a period of satisfactory sterility test results will form part of the acceptance criteria. There may be cases when a new product is only a minor variation, from the sterility assurance point of view, and existing sterility test data from other products could be considered as relevant.

3.7 A risk analysis of the sterility assurance system focused on an evaluation of releasing non-sterilised products should be performed.

3.8 The manufacturer should have a history of good GMP compliance.

3.9 The history of non sterility of products and of results of sterility tests carried out on the product in question together with products processed through the same or a similar

sterility assurance system should be taken into consideration when evaluating GMP compliance.

3.10 A qualified experienced sterility assurance engineer and a qualified microbiologist should normally be present on the site of production and sterilization.

3.11 The design and original validation of the product should ensure that integrity can be maintained under all relevant conditions.

3.12 The change control system should require review of change by sterility assurance personnel.

3.13 There should be a system to control microbiological contamination in the product before sterilisation.

3.14 There should be no possibility for mix ups between sterilised and non-sterilised products. Physical barriers or validated electronic systems may provide such assurance.

3.15 The sterilization records should be checked for compliance to specification by at least two independent systems. These systems may consist of two people or a validated computer system plus a person.

3.16 The following additional items should be confirmed prior to release of each batch of product:

- All planned maintenance and routine checks have been completed in the sterilizer used.
- All repairs and modifications have been approved by the sterility assurance engineer and microbiologist.
- All instrumentation was in calibration.
- The sterilizer had a current validation for the product load processed.

3.17. Once parametric release has been granted, decisions for release or rejection of a batch should be based on the approved specifications. Non-compliance with the specification for parametric release cannot be overruled by a pass of a sterility test.

4. Glossary

Parametric release

A system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing process and on the compliance with specific GMP requirements related to Parametric Release.

Sterility assurance system

The sum total of the arrangements made to assure the sterility of products. For terminally sterilized products these typically include the following stages:

a) Product design;
b) Knowledge of and, if possible, control of the microbiological condition of starting materials and process aids (e.g. gases and lubricants).
c) Control of the contamination of the process of manufacture to avoid the ingress of microorganisms and their multiplication in the product. This is usually accomplished by cleaning and sanitization of product contact surfaces, prevention of aerial contamination by handling in clean rooms, use of process control time limits and, if applicable, filtration stages.
d) Prevention of mix up between sterile and non sterile product streams.
e) Maintenance of product integrity;
f) The sterilisation process;
g) The totality of the Quality System that contains the Sterility Assurance System e.g. change control, training, written procedures, release checks, planned preventative maintenance, failure mode analysis, prevention of human error, validation calibration, etc.

ANNEX 19

REFERENCE AND RETENTION SAMPLES

1. Scope

1.1 This Annex to the Guideline on Good Manufacturing Practice for Medicinal Products ("the GMP Guideline") gives guidance on the taking and holding of reference samples of starting materials, packaging materials or finished products and retention samples of the finished product.

1.2 Specific requirements for investigational medicinal products are given in Annex 13 to the Guideline.

2. Principle

2.1 Samples are retained to fulfil two purposes; firstly to provide a sample for analytical testing and secondly to provide a specimen of the fully finished product. Samples may therefore fall into two categories:

Reference sample: a sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being analysed should the need arise during the shelf life of the batch concerned. Where stability permits, reference samples from critical intermediate stages (e.g. those requiring analytical testing and release) or intermediates, that are transported outside of the manufacturer's control, should be kept.

Retention sample: a sample of a fully packaged unit from a batch of finished product. It is stored for identification purposes. For example, presentation, packaging, labelling, patient information leaflet, batch number, expiry date should the need arise during the shelf life of the batch concerned. There may be exceptional circumstances where this requirement can be met without retention of duplicate samples e.g. where small amounts of a batch are packaged for different markets or in the production of very expensive medicinal products. For finished products, in many instances the reference and retention samples will be presented identically, i.e. as fully packaged units. In such circumstances, reference and retention samples may be regarded as interchangeable.

2.2 It is necessary for the manufacturer, importer or site of batch release, as specified under section 7 and 8, to keep reference and/or retention samples from each batch of finished product and, for the manufacturer to keep a reference sample from a batch of starting material (subject to certain exceptions – see 3.2 below) and/or intermediate product. Each packaging site should keep reference samples of each batch of primary and printed packaging materials. Availability of printed materials as part of the reference and/or retention sample of the finished product can be accepted.

2.3 The reference and/or retention samples serve as a record of the batch of finished product or starting material and can be assessed in the event of, for example, a dosage form quality complaint, a query relating to compliance with the marketing authorisation, a labelling/packaging query or a pharmacovigilance report.

2.4 Records of traceability of samples should be maintained and be available for review by competent authorities.

3. Duration of storage

3.1 Reference and retention samples from each batch of finished product should be retained for at least one year after the expiry date. The reference sample should be contained in its finished primary packaging or in packaging composed of the same material as the primary container in which the product is marketed.

3.2 Samples of starting materials (other than solvents, gases or water used in the manufacturing process) shall be retained for at least two years after the release of product. That period may be shortened if the period of stability of the material, as indicated in the relevant specification, is shorter. Packaging materials should be retained for the duration of the shelf life of the finished product concerned.

4. Size of Reference and Retention Samples

4.1 The reference sample should be of sufficient size to permit the carrying out, on, at least, two occasions, of the full analytical controls on the batch in accordance with the Marketing Authorisation File which has been assessed and approved by the relevant Competent Authority / Authorities. Where it is necessary to do so, unopened packs should be used when carrying out each set of analytical controls. Any proposed exception to this should be justified to, and agreed with, the relevant competent authority.

4.2 Where applicable, national requirements relating to the size of reference samples and, if necessary, retention samples, should be followed.

4.3 Reference samples should be representative of the batch of starting material, intermediate product or finished product 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). Where a batch is packaged in two, or more, distinct packaging operations, at least one retention sample should be taken from each individual packaging operation. Any proposed exception to this should be justified to, and agreed with, the relevant competent authority.

4.4 It should be ensured that all necessary analytical materials and equipment are still available, or are readily obtainable, in order to carry out all tests given in the specification until one year after expiry of the last batch manufactured.

5. Storage conditions

5.1 Storage of reference samples of finished products and active substances should be in accordance with the current version of the Note for Guidance on Declaration of Storage Conditions for Medicinal Products and Active Substances.

5.2 Storage conditions should be in accordance with the marketing authorisation (e.g. refrigerated storage where relevant).

6. Written agreements

6.1 Where the marketing authorisation holder is not the same legal entity as the site(s) responsible for batch release within the EEA, the responsibility for taking and storage of reference/retention samples should be defined in a written agreement between the two parties in accordance with Chapter 7 of the EC Guide to Good Manufacturing Practice. This applies also where any manufacturing or batch release activity is carried out at a site other than that with overall responsibility for the batch on the EEA market and the arrangements between each different site for the taking and keeping of reference and retention samples should be defined in a written agreement.

6.2 The Qualified Person who certifies a batch for sale should ensure that all relevant reference and retention samples are accessible at all reasonable times. Where necessary, the arrangements for such access should be defined in a written agreement.

6.3 Where more than one site is involved in the manufacture of a finished product, the availability of written agreements is key to controlling the taking and location of reference and retention samples.

7. Reference samples – general points

7.1 Reference samples are for the purpose of analysis and, therefore, should be conveniently available to a laboratory with validated methodology. For starting materials used for medicinal products manufactured within the EEA, this is the original site of manufacture of the finished product. For finished products manufactured within the EEA, this is the original site of manufacture.

7.2 For finished products manufactured by a manufacturer in a country outside the EEA;

7.2.1 Where an operational Mutual Recognition Agreement (MRA) is in place, the reference samples may be taken and stored at the site of manufacture. This should be covered in a written agreement (as referred to in section 6 above) between the importer/site of batch release and the manufacturer located outside the EEA.

7.2.2 Where an operational MRA is not in place, reference samples of the finished medicinal product should be taken and stored at an authorised manufacturer located within the EEA. These samples should be taken in accordance with written agreement(s) between all of the parties concerned. The samples should, preferably, be stored at the location where testing on importation has been performed.

7.2.3 Reference samples of starting materials and packaging materials should be kept at the original site at which they were used in the manufacture of the medicinal product.

8. Retention samples – general points

8.1 A retention sample should represent a batch of finished products as distributed in the EEA and may need to be examined in order to confirm non-technical attributes for compliance with the marketing authorisation or EU legislation. Therefore, retention samples should in all cases be located within the EEA. These should preferably be stored at the site where the Qualified Person (QP) certifying the finished product batch is located.

8.2 In accordance with 8.1 above, where an operational MRA is in place and reference samples are retained at a manufacturer located in a country outside the EEA (section 7.2.2 above), separate retention samples should be kept within the EEA.

8.3 Retention samples should be stored at the premises of an authorised manufacturer in order to permit ready access by the Competent Authority.

8.4 Where more than one manufacturing site within the EEA is involved in the manufacture importation/packaging/testing/batch release, as appropriate of a product, the responsibility for taking and storage of retention samples should be defined in a written agreement(s) between the parties concerned.

9. Reference and retention samples for parallel imported/parallel distributed products

9.1 Where the secondary packaging is not opened, only the packaging material used needs to be retained, as there is no, or little, risk of product mix up.

9.2 Where the secondary packaging is opened, for example, to replace the carton or patient information leaflet, then only leaflet, then one retention sample, per packaging operation, containing the product should be taken, as there is a risk of product mix-up during the assembly process. It is important to be able to identify quickly who is responsible in the event of a mix-up (original manufacturer or parallel import assembler), as it would affect the extent of any resulting recall.

10. Reference and Retention Samples in the Case of Closedown of a Manufacturer

10.1 Where a manufacturer closes down and the manufacturing authorisation is surrendered, revoked, or ceases to exist, it is probable that many unexpired batches of medicinal products manufactured by that manufacturer remain on the market. In order for those batches to remain on the market, the manufacturer should make detailed arrangements for

transfer of reference and retention samples (and relevant GMP documentation) to an authorised storage site. The manufacturer should satisfy the Competent Authority that the arrangements for storage are satisfactory and that the samples can, if necessary, be readily accessed and analysed.

10.2 If the manufacturer is not in a position to make the necessary arrangements this may be delegated to another manufacturer. The Marketing Authorisation holder (MAH) is responsible for such delegation and for the provision of all necessary information to the Competent Authority. In addition, the MAH should, in relation to the suitability of the proposed arrangements for storage of reference and retention samples, consult with the competent authority of each Member State in which any unexpired batch has been placed on the market. These requirements apply also in the event of the closedown of a manufacture located outside the EEA. In such instances, the importer has a particular responsibility to ensure that satisfactory arrangements are put in place and that the competent authority/authorities is/are consulted.

GLOSSARY

Definitions given below apply to the words as used in this Guideline. They may have different meanings in other contexts.

Air-lock

An enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when they need to be entered. An air-lock is designed for and used by either people or goods.

Batch (or lot)

A defined quantity of starting material, packaging material or product processed in a single process or series of processes so that it could be expected to be homogeneous.
Note: To complete certain stages of manufacture, it may be necessary to divide a batch into a number of subbatches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterised by its intended homogeneity.

Batch in the context of finished product control: an entity containing all units of a pharmaceutical form, which are made from the same initial mass of material and have undergone a single series of manufacturing and/or sterilisation operations or, in the case of a continuous production process, all the units manufactured in a given period of time (Section 3.2.2.5 of Order of the Minister of Public Health No. 906/2006 on approval of the Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products, transposing the provisions of Directive 2003/63/EC, amending Directive 2001/83/EC).

Batch number (or lot number)

A distinctive combination of numbers and/or letters which specifically identifies a batch.

Biogenerator

A contained system, such as a fermenter, into which biological agents are introduced along with other materials so as to effect their multiplication or their production of other substances by reaction with the other materials. Bio generators are generally fitted with devices for regulation, control, connection, material addition and material withdrawal.

Biological agents

Micro-organisms, including genetically engineered micro-organisms, cell cultures and endoparasites, whether pathogenic or not.

Bulk product

Any product which has completed all processing stages up to, but not including, final packaging.

Calibration

The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

Cell bank

Cell bank system: A cell bank system is a system whereby successive batches of a product are manufactured by culture in cells derived from the same master cell bank. A number of containers from the master cell bank are used to prepare a working cell bank. The cell bank system is validated for a passage level or number of population doublings beyond that achieved during routine production.

Master cell bank: A culture of (fully characterised) cells distributed into containers in a single operation, processed together in such a manner as to ensure uniformity and stored in such a manner as to ensure stability. A master cell bank is usually stored at - 70°C or lower.

Working cell bank: A culture of cells derived from the master cell bank and intended for use in the preparation of production cell cultures. The working cell bank is usually stored at -70°C or lower.

Cell culture

The result from the "*in-vitro"* growth of cells isolated from multicellular organisms.

Clean area

An area with defined environmental control of particulate and microbial contamination constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

Note: The different degrees of environmental control are defined in the Annex on the Manufacture of sterile medicinal products.

Clean/contained area

An area constructed and operated in such a manner that will achieve the aims of both a clean area and a contained area at the same time.

Computerised system

A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.

Contained area

An area constructed and operated in such a manner (and equipped with appropriate air handling and filtration) so as to prevent contamination of the external environment by biological agents from within the area.

Containment

The action of confining a biological agent or other entity within a defined space.

Primary containment: A system of containment which prevents the escape of a biological agent into the immediate working environment. It involves the use of closed containers or safety biological cabinets along with secure operating procedures.

Secondary containment: A system of containment which prevents the escape of a biological agent into the external environment or into other working areas. It involves the use of

rooms with specially designed air handling, the existence of airlocks and/or sterilisers for the exit of materials and secure operating procedures. In many cases it may add to the effectiveness of primary containment.

Controlled area

An area constructed and operated in such a manner that some attempt is made to control the introduction of potential contamination (an air supply approximating to grade D may be appropriate), and the consequences of accidental release of living organisms. The level of control exercised should reflect the nature of the organism employed in the process. At a minimum, the area should be maintained at a pressure negative to the immediate external environment and allow for the efficient removal of small quantities of airborne contaminants.

Cross contamination

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

Crude plant

Fresh or dried medicinal plant or parts thereof.

Exotic organism

A biological agent where either the corresponding disease does not exist in a given country or geographical area, or where the disease is the subject of prophylactic measures or an eradication programme undertaken in the given country or geographical area.

Finished product

A medicinal product which has undergone all stages of production, including packaging in its final container.

Herbal medicinal product

Medicinal product containing, as active ingredients, exclusively plant material and/or vegetable drug preparations.

Infected

Contaminated with extraneous biological agents and therefore capable of spreading infection.

In-process control

Checks performed during production in order to monitor and if necessary to adjust the process to make sure that the product is compliant with its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate product

Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

Manufacture

All operations of purchase of materials and products, Production, Quality Control, release, storage, distribution of medicinal products and the related controls.

Manufacturer

Holder of a Manufacturing Authorisation as described in Article 748 of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product.

Medicinal plant

Plant (the whole or part of) which is used for medicinal purposes.

Medicinal product

Any substance or combination of substances presented for treating or preventing disease in human beings or animals.

Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product. (Art. 695, point 1 of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product).

Packaging

All operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product.

Note: Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not finally packaged, primary containers.

Packaging material

Any material employed in the packaging of a medicinal product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the medicinal product.

Production

All operations involved in the preparation of a medicinal product, from receipt of materials, through processing and packaging, to its completion as a finished product.

Procedures

Description of the operations to be carried out, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of a medicinal product.

Qualification

Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification.

Quality control

See Chapter 1.

Quarantine

The status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or refusal.

Radiopharmaceutical

"Radiopharmaceutical" shall mean any medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) included for medical purposes – Art. 695 (5) of Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product.

Record

See Chapter 4.

Seed lot

Seed lot system: A seed lot system is a system according to which successive batches of a product are derived from the same master seed lot at a given passage level. For routine production, a working seed lot is prepared from the master seed lot. The finished product is derived from the working seed lot and has not undergone more passages from the master seed lot than the vaccine shown in clinical studies to be satisfactory with respect to safety and efficacy. The origin and the passage history of the master seed lot and the working seed lot are recorded.

Master seed lot: A culture of a micro-organism distributed from a single bulk into containers in a single operation in such a manner as to ensure uniformity, to prevent contamination and to ensure stability. A master seed lot in liquid form is usually stored at or below - 70°C. A freeze-dried master seed lot is stored at a temperature known to ensure stability.

Working seed lot: A culture of a micro-organism derived from the master seed lot and intended for use in production. Working seed lots are distributed into containers and stored as described above for master seed lots.

Starting material

Any substance used in the production of a medicinal product, but excluding packaging materials.

Reconciliation

A comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used.

Recovery

The introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture.

Reprocessing

The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.

Return

Sending back to the manufacturer or distributor of a medicinal product which may or may not present a quality defect.

Specification

See Chapter 4.

Sterility

Sterility is the absence of living organisms. The conditions of the sterility test are given in the European Pharmacopoeia.

System

Is used in the sense of a regulated pattern of interacting activities and techniques which are united to form an organised whole.

Validation

Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).