EudraLex - Volume 4 - Good Manufacturing Practice (GMP) guidelines

Part I - Basic Requirements for Medicinal Products

- Chapter 1 - Pharmaceutical Quality System (into operation since 31 January 2013)
- Chapter 2 - Personnel (into operation since 16 February 2014)
- Chapter 3 - Premise and Equipment (into operation since 1 March 2015)
    - See transitional arrangement for toxicological evaluation on page 1 of Chapter 3
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- Chapter 4 - Documentation (January 2011)
- Chapter 5 - Production (into operation since 1 March 2015)
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- Chapter 6 - Quality Control (into operation since 1 October 2014)
- Chapter 7 - Outsourced activities (into operation since 31 January 2013)
- Chapter 8 - Complaints and Product Recall (into operation since 1 March 2015)
- Chapter 9 - Self Inspection

Annexes

Annex 1	New - Manufacture of Sterile Medicinal Products - The deadline for coming into operation of Annex 1 is 25 August 2023, except for point 8.123 which is postponed until 25 August 2024 Manufacture of Sterile Medicinal Products (previous version)
Annex 2	New - Manufacture of Biological active substances and Medicinal Products for Human Use (into operation since 26 June 2018) *Annex 2 is no longer applicable to Advanced Therapy Medicinal Products to which applies the Commission guideline on Good Manufacturing Practice for Advanced Therapy Medicinal Products, published in Part IV of Eudralex Volume 4 and operational as of 22 May 2018.*
Annex 3	Manufacture of Radiopharmaceuticals
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
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Annex 11	Computerised Systems (revision January 2011)
Annex 12	Use of Ionising Radiation in the Manufacture of Medicinal Products
Annex 13	Manufacture of Investigational Medicinal Products Detailed Commission guideline of 8 December 2017 on the good manufacturing practice for investigational medicinal products pursuant to the second paragraph of the Article 63(1) of Regulation (EU) No 536/2014 (applicable as from the date of entry into application of Regulation (EU) No 536/2014 on Clinical Trials)
Annex 14	Manufacture of Products derived from Human Blood or Human Plasma (May 2011)
Annex 15	Qualification and validation (into operation since 1 October 2015)
Annex 16	Certification by a Qualified Person and Batch Release (into operation since 15 April 2016)
Annex 17	New - Parametric release (Deadline for coming into operation: 26 December 2018) Further information on the consultation can be found here.
Annex 19	Reference and Retention Samples
Annex 20	Quality Risk Management
Annex 21	Importation of medicinal products

Note: Annex 18 formed the basis of should form the basis of the detailed guidelines to create Part II of the Eudralex Volume 4 GMP Guide. ***Therefore no Annex 18.***

Chapter 1
Pharmaceutical Quality System

Pharmaceutical Quality System Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use. Status of the document: revision 3 Reasons for changes: Amendments to the text of Chapter 1 have been made in order to align with the concepts and terminology described in the ICH Q10 tripartite guideline on Pharmaceutical Quality System. The title of the chapter itself is also changed accordingly.
Deadline for coming into operation: 31 January 2013

Principle

The holder of a Manufacturing Authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation or Clinical Trial Authorisation, as appropriate and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by its distributors. To achieve this quality objective reliably there must be a comprehensively designed and correctly implemented Pharmaceutical Quality System1 incorporating Good Manufacturing Practice and Quality Risk Management. It should be fully documented and its effectiveness monitored. All parts of the Pharmaceutical Quality System should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. There are additional legal responsibilities for the holder of the Manufacturing Authorisation and for the Qualified Person(s). The basic concepts of Quality Management, Good Manufacturing Practice and Quality Risk Management are inter-related. They are described here in order to emphasise their relationships and their fundamental importance to the production and control of medicinal products.

Pharmaceutical Quality System[1]

1.1 Quality Management is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organised arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Management therefore incorporates Good Manufacturing Practice.

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

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

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

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

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

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

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

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

(v) Managerial responsibilities are clearly specified;

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

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

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

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

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

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

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

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

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

(xv) Medicinal products are not sold or supplied before a Qualified Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorisation and any other regulations relevant to the production, control and release of medicinal products;

(xvi) Satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;

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

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

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

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

Good Manufacturing Practice for Medicinal Products

1.8 Good Manufacturing Practice is that part of Quality Management which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorisation, Clinical Trial Authorisation or product specification. Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

(i) All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;

(ii) Critical steps of manufacturing processes and significant changes to the process are validated;

(iii) All necessary facilities for GMP are provided including:

- Appropriately qualified and trained personnel;
- Adequate premises and space;
- Suitable equipment and services;
- Correct materials, containers and labels;
- Approved procedures and instructions, in accordance with the Pharmaceutical Quality System;
- Suitable storage and transport;

(iv) Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;

(v) Procedures are carried out correctly and operators are trained to do so;

(vi) Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected.

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

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

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

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

(xi) Complaints about products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent reoccurrence.

Quality Control

1.9 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications and testing, and with the organisation, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. The basic requirements of Quality Control are that:

(i) Adequate facilities, trained personnel and approved procedures are available for sampling and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;

(ii) Samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by approved personnel and methods;

(iii) Test methods are validated;

(iv) Records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated;

(v) The finished products contain active ingredients complying with the qualitative and quantitative composition of the Marketing Authorisation or clinical trial authorisation, are of the purity required, and are enclosed within their proper containers and correctly labelled;

(vi) Records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;

(vii) No batch of product is released for sale or supply prior to certification by a Qualified Person that it is in accordance with the requirements of the relevant authorisations in accordance with annex 16;

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

Product Quality Review

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

(i) A review of starting materials including packaging materials used in the product, especially those from new sources and in particular the review of supply chain traceability of active substances.

(ii) A review of critical in-process controls and finished product results.

(iii) A review of all batches that failed to meet established specification(s) and their investigation.

(iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken.

(v) A review of all changes carried out to the processes or analytical methods.

(vi) A review of Marketing Authorisation variations submitted, granted or refused, including those for third country (export only) dossiers.

(vii) A review of the results of the stability monitoring programme and any adverse trends.

(viii) A review of all quality-related returns, complaints and recalls and the investigations performed at the time.

(ix) A review of adequacy of any other previous product process or equipment corrective actions.

(x) For new marketing authorisations and variations to marketing authorisations, a review of post-marketing commitments.

(xi) The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.

(xii) A review of any contractual arrangements as defined in Chapter 7 to ensure that they are up to date.

1.11 The manufacturer and, where different, marketing authorisation holder should evaluate the results of the review and an assessment made as to whether corrective and preventive action or any revalidation should be undertaken, under the Pharmaceutical Quality System. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. where scientifically justified.

Where the marketing authorisation holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the product quality review.

Quality Risk Management

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

1.13 The principles of quality risk management are that:

(i) The evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient

(ii) The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk Examples of the processes and applications of quality risk management can be found inter alia in ICH Q9 which is reproduced in Part III of the Guide.

Chapter 2
Personnel

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use. Status of the document: Revisiona Reasons for changes: Changes have been made in order to integrate the principles of "Pharmaceutical Quality System" as described in the ICH Q10 tripartite guideline. A section has been added on consultants
Deadline for coming into operation: 16 February 2014

Principle

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

General

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

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

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

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

Key Personnel

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

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

(a) for medicinal products manufactured within the European Union, a Qualified Person must ensure that each batch has been manufactured and checked in compliance with the laws in force in that Member State and in accordance with the requirements of the marketing authorisation[2];

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

The persons responsible for these duties must meet the qualification requirements laid down in Article 49[3] of the same Directive, they shall be permanently and continuously at the disposal of the holder of the Manufacturing Authorisation to carry out their responsibilities.

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

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

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

[3] Article 53 of Directive 2001/82/EC

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

(i) To ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;

(ii) To approve the instructions relating to production operations and to ensure their strict implementation;

(iii) To ensure that the production records are evaluated and signed by an authorised person;

(iv) To ensure the qualification and maintenance of his department, premises and equipment;

(v) To ensure that the appropriate validations are done;

(vi) To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

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

(i) To approve or reject, as he sees fit, starting materials, packaging materials, intermediate, bulk and finished products;

(ii) To ensure that all necessary testing is carried out and the associated records evaluated;

(iii) To approve specifications, sampling instructions, test methods and other Quality Control procedures;

(iv) To approve and monitor any contract analysts;

(v) To ensure the qualification and maintenance of his department, premises and equipment;

(vi) To ensure that the appropriate validations are done;

(vii) To ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

Other duties of Quality Control are summarised in Chapter 6.

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

(i) The authorisation of written procedures and other documents, including amendments;

(ii) The monitoring and control of the manufacturing environment;

(iii) Plant hygiene;

(iv) Process validation;

(v) Training;

(vi) The approval and monitoring of suppliers of materials;

(vii) The approval and monitoring of contract manufacturers and providers of other GMP related outsourced activities;

(viii) The designation and monitoring of storage conditions for materials and products;

(ix) The retention of records;

(x) The monitoring of compliance with the requirements of Good Manufacturing Practice;

(xi) The inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality;

(xii) Participation in management reviews of process performance, product quality and of the quality management system and advocating continual improvement

(xiii) Ensuring that a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management.

Training

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

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

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

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

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

Personnel Hygiene

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

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

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

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

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

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

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

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

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

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

Chapter 3
Premises and Equipment

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

Status of the document: Revision*

> * In January 2015 the deadline for coming into operation was adapted with regard to the toxicological evaluation to align with the coming effect of the EMA guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.

Reasons for changes: The only change is to section 6 as part of the improved guidance on prevention of cross-contamination involving also Chapter 5.

Deadline for coming into operation: 1 March 2015. However, the toxicological evaluation mentioned in section 6 is to be carried out:

- from 1 June 2015 onwards for any medicinal product newly introduced into shared manufacturing facilities;
- before 1 December 2015 for medicinal products already produced in a shared manufacturing facility producing only medicinal products for human use or both producing medicinal products for human use and veterinary medicinal products on 31 May 2015;
- before 1 June 2016 for veterinary medicinal products already produced in a shared manufacturing facility producing only veterinary medicinal products on 31 May 2015

PRINCIPLE

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

PREMISES

General

3.1 Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

3.2 Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

3.3 Lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.

3.4 Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

3.5 Steps should be taken in order to prevent the entry of unauthorised people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

Production Area

3.6 Cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities. The measures to prevent cross-contamination should be commensurate with the risks. Quality Risk Management principles should be used to assess and control the risks. Depending of the level of risk, it may be necessary to dedicate premises and equipment for manufacturing and/or packaging operations to control the risk presented by some medicinal products.

Dedicated facilities are required for manufacturing when a medicinal product presents a risk because:

i. the risk cannot be adequately controlled by operational and/ or technical measures,

ii. scientific data from the toxicological evaluation does not support a controllable risk (e.g. allergenic potential from highly sensitising materials such as beta lactams) or

iii. relevant residue limits, derived from the toxicological evaluation, cannot be satisfactorily determined by a validated analytical method.

Further guidance can be found in Chapter 5 and in Annexes 2, 3, 4, 5 & 6

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 Pipe work, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

3.11 Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.

3.12 Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.

3.13 Weighing of starting materials usually should be carried out in a separate weighing room designed for such 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 to production.

Storage Areas

3.18 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, products in quarantine, released, rejected, returned or recalled.

3.19 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored.

3.20 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

3.21 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine should give equivalent security.

3.22 There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

3.23 Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.

3.24 Highly active materials or products should be stored in safe and secure areas.

3.25 Printed packaging materials are considered critical to the conformity of the medicinal product and special attention should be paid to the safe and secure storage of these materials.

Quality Control Areas

3.26 Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, microbiologicals and radioisotopes, which should also be separated from each other.

3.27 Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

3.28 Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.

3.29 Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

Ancillary Areas

3.30 Rest and refreshment rooms should be separate from other areas.

3.31 Facilities for changing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.

3.32 Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

3.33 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

EQUIPMENT

3.34 Manufacturing equipment should be designed, located and maintained to suit its intended purpose.

3.35 Repair and maintenance operations should not present any hazard to the quality of the products.

3.36 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.

3.37 Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.

3.38 Equipment should be installed in such a way as to prevent any risk of error or of contamination.

3.39 Production equipment should not present any hazard to products. Parts of 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 pipe work 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

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

Status of the document: revision 1

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

Deadline for coming into operation: 30 June 2011

PRINCIPLE

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

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

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

REQUIRED GMP DOCUMENTATION (BY TYPE):

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

INSTRUCTIONS (DIRECTIONS, OR REQUIREMENTS) TYPE:

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

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

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

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

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

RECORD/REPORT TYPE:

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

Certificates Of Analysis:
Provide a summary of testing results on samples of products or materials[1] together with the evaluation for compliance to a stated specification[1].

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

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.

Generation and Control of Documentation

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

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

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

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

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

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

Good Documentation Practices

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

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

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

Retention of Documents

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

4.11 Specific requirements apply to batch documentation which must be kept for one year after expiry of the batch to which it relates or at least five years after certification of the batch by the Qualified Person, whichever is the longer. For investigational medicinal products, the batch documentation must be kept for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch

was used. Other requirements for retention of documentation may be described in legislation in relation to specific types of products (e.g. Advanced Therapy Medicinal Products) and specify that longer retention periods be applied to certain documents.

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

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

Specifications

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

Specifications for Starting and Packaging Materials

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

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

Specifications For Intermediate and Bulk Products

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

Specifications for Finished Products

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

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

Manufacturing Formula and Processing Instructions

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

4.17 The Manufacturing Formula should include:

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

4.18 The Processing Instructions should include:

a. A statement of the processing location and the principal equipment to be used;
b. The methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);
c. Checks that the equipment and workstation 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 should exist. These should include, or have a reference to, the following:

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

Batch Processing Record

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

e) The name and batch number of the product;
f) Dates and times of commencement, of significant intermediate stages and of completion of production;
g) 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;
h) 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);
i) Any relevant processing operation or event and major equipment used;
j) A record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
k) The product yield obtained at different and pertinent stages of manufacture;
l) Notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions;
m) Approval by the person responsible for the processing operations.

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

Batch Packaging Record

4.21 A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions. The batch packaging record should contain the following information:

n) The name and batch number of the product,
o) The date(s) and times of the packaging operations;
p) 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;
q) Records of checks for identity and conformity with the packaging instructions, including the results of in-process controls;
r) Details of the packaging operations carried out, including references to equipment and the packaging lines used;
s) 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;
t) 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.
i. Where there are there are robust electronic controls in place during packaging there may be justification for not including this information
u) Approval by the person responsible for the packaging operations

Procedures and records

Receipt

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

4.23 The records of the receipts should include:

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

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

Sampling

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

Testing

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

Other

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

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

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

- Validation and qualification of processes, equipment and systems;
- Equipment assembly and calibration;
- Technology transfer;
- Maintenance, cleaning and sanitation;
- Personnel matters including signature lists, training in GMP and technical matters, clothing and hygiene and verification of the effectiveness of training.
- Environmental monitoring;
- Pest control;
- Complaints;
- Recalls;
- Returns;
- Change control;
- Investigations into deviations and non-conformances;
- Internal quality/GMP compliance audits;
- Summaries of records where appropriate (e.g. product quality review);
- Supplier audits.

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

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

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

Chapter 5
Production

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

Status of the document**:** Revision[a].

a. In January 2015 the deadline for coming into operation was adapted with regard to the toxicological evaluation to align with the coming effect of the EMA guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. Furthermore, correction of the reference in footnote 2 took place.

Commission Européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel – Belgium. Telephone: (32-2) 299 11 11

Reasons for changes: Changes have been made to sections 17 to 21, including adding a new section, to improve the guidance on prevention of cross-contamination and to refer to toxicological assessment. Changes were also introduced in sections 27 to 30, including adding a new section, on the qualification of suppliers in order to reflect the legal obligation of manufacturing authorisation holders to ensure that active substances are produced in accordance with GMP. The changes include supply chain traceability. Sections 35 and 36 are inserted to clarify and harmonise expectations of manufacturers regarding the testing of starting materials while section 71 introduces guidance on notification of restrictions in supply.
Deadline for coming into operation: 1 March 2015. However, the toxicological evaluation mentioned in section 20 has to be carried out:

- from 1 June 2015 onwards for any medicinal product newly introduced into shared manufacturing facilities;
- before 1 December 2015 for medicinal products already produced in a shared manufacturing facility producing only medicinal products for human use or producing both medicinal products for human use and veterinary medicinal products on 31 May 2015;
- before 1 June 2016 for veterinary medicinal products already produced in a shared manufacturing facility producing only veterinary medicinal products on 31 May 2015.

a. In January 2015 the deadline for coming into operation was adapted with regard to the toxicological evaluation to align with the coming effect of the EMA guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. Furthermore, correction of the reference in footnote 2 took place.

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Principle

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

General

5.1 Production should be performed and supervised by competent people.

5.2 All handling of materials and products, such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

5.3 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled with the prescribed data.

5.4 Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded and reported to the Quality Control Department.

5.5 Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

5.6 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

5.7 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.

5.8 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

5.9 Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.

5.10 At every stage of processing, products and materials should be protected from microbial and other contamination.

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

5.12 At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

5.13 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example, quarantined, accepted, rejected, clean).

5.14 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

5.15 Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control department when appropriate.

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

Prevention of cross-contamination in production

5.17 Normally, the production of non-medicinal products should be avoided in areas and with equipment destined for the production of medicinal products but, where justified, could be allowed where the measures to prevent cross-contamination with medicinal products described below and in Chapter 3 can be applied. The production and/or storage of technical poisons, such as pesticides (except where these are used for manufacture of medicinal products) and herbicides, should not be allowed in areas used for the manufacture and / or storage of medicinal products.

5.18 Contamination of a starting material or of a product by another material or product should be prevented. This risk of accidental cross-contamination resulting from the uncontrolled release of dust, gases, vapours, aerosols, genetic material or organisms from active substances, other starting materials, and products in process, from residues on equipment, and from operators' clothing should be assessed. The significance of this risk varies with the nature of the contaminant and that of the product being contaminated. Products in which cross-contamination is likely to be most significant are those administered by injection and those given over a long time. However, contamination of all products poses a risk to patient safety dependent on the nature and extent of contamination.

5.19 Cross-contamination should be prevented by attention to design of the premises and equipment as described in Chapter 3. This should be supported by attention to process design and implementation of any relevant technical or organizational measures, including effective and reproducible cleaning processes to control risk of cross-contamination.

5.20 A Quality Risk Management process, which includes a potency and toxicological evaluation, should be used to assess and control the cross-contamination risks presented by the products manufactured. Factors including; facility/equipment design and use, personnel and material flow, microbiological controls, physico-chemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the relevant limits established from the evaluation of the products should also be taken into account. The outcome of the Quality Risk Management process should be the basis for determining the necessity for and extent to which premises and equipment should be dedicated to a particular product or product family. This may include dedicating specific product contact parts or dedication of the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a segregated, self contained production area within a multiproduct facility, where justified.

5.21 The outcome of the Quality Risk Management process should be the basis for determining the extent of technical and organisational measures required to control risks for cross-contamination. These could include, but are not limited to, the following:

Technical Measures

i. Dedicated manufacturing facility (premises and equipment);
ii. Self-contained production areas having separate processing equipment and separate heating, ventilation and air-conditioning (HVAC) systems. It may also be desirable to isolate certain utilities from those used in other areas;

iii. Design of manufacturing process, premises and equipment to minimize opportunities for cross-contamination during processing, maintenance and cleaning;
iv. Use of “closed systems” for processing and material/product transfer between equipment;
v. Use of physical barrier systems, including isolators, as containment measures;
vi. Controlled removal of dust close to source of the contaminant e.g. through localised extraction;
vii. Dedication of equipment, dedication of product contact parts or dedication of selected parts which are harder to clean (e.g. filters), dedication of maintenance tools;
viii. Use of single use disposable technologies;
ix. Use of equipment designed for ease of cleaning;
x. Appropriate use of air-locks and pressure cascade to confine potential airborne contaminant within a specified area;
xi. Minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
xii. Use of automatic clean in place systems of validated effectiveness;
xiii. For common general wash areas, separation of equipment washing, drying and storage areas.

Organisational Measures

i. Dedicating the whole manufacturing facility or a self contained production area on a campaign basis (dedicated by separation in time) followed by a cleaning process of validated effectiveness;
ii. Keeping specific protective clothing inside areas where products with high risk of cross-contamination are processed;
iii. Cleaning verification after each product campaign should be considered as a detectability tool to support effectiveness of the Quality Risk Management approach for products deemed to present higher risk;
iv. Depending on the contamination risk, verification of cleaning of non product contact surfaces and monitoring of air within the manufacturing area and/or adjoining areas in order to demonstrate effectiveness of control measures against airborne contamination or contamination by mechanical transfer;
v. Specific measures for waste handling, contaminated rinsing water and soiled gowning;
vi. Recording of spills, accidental events or deviations from procedures;
vii. Design of cleaning processes for premises and equipment such that the cleaning processes in themselves do not present a cross-contamination risk;
viii. Design of detailed records for cleaning processes to assure completion of cleaning in accordance with approved procedures and use of cleaning status labels on equipment and manufacturing areas;
ix. Use of common general wash areas on a campaign basis;
x. Supervision of working behaviour to ensure training effectiveness and compliance with the relevant procedural controls.

5.22 Measures to prevent cross-contamination and their effectiveness should be reviewed periodically according to set procedures.

Validation

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

5.24 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

5.25 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process, should be validated.

5.26 Processes and procedures should undergo periodic critical re-validation to ensure that they remain capable of achieving the intended results.

Starting materials

5.27 The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance, should be documented as part of the pharmaceutical quality system. The level of supervision should be proportionate to the risks posed by the individual materials, taking account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the medicinal product. The supporting evidence for each supplier / material approval should be maintained. Staff involved in these activities should have a current knowledge of the suppliers, the supply chain and the associated risks involved. Where possible, starting materials should be purchased directly from the manufacturer of the starting material.

5.28 The quality requirements established by the manufacturer for the starting materials should be discussed and agreed with the suppliers. Appropriate aspects of the production, testing and control, including handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures should be documented in a formal quality agreement or specification.

5.29 For the approval and maintenance of suppliers of active substances and excipients, the following is required:

Active substances[1]

Supply chain traceability should be established and the associated risks, from active substance starting materials to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance.

The supply chain and traceability records for each active substance (including active substance starting materials) should be available and be retained by the EEA based manufacturer or importer of the medicinal product.

[1] Specific requirement apply to the importation of active substances to be used in the manufacture of medicinal products for human use in article 46b of Directive 2001/83/EC.

Audits should be carried out at the manufacturers and distributors of active substances to confirm that they comply with the relevant good manufacturing practice and good distribution practice requirements. The holder of the manufacturing authorisation shall verify such compliance either by himself or through an entity acting on his behalf under a contract. For veterinary medicinal products, audits should be conducted based on risk.

Audits should be of an appropriate duration and scope to ensure that a full and clear assessment of GMP is made; consideration should be given to potential cross- contamination from other materials on site. The report should fully reflect what was done and seen on the audit with any deficiencies clearly identified. Any required corrective and preventive actions should be implemented.

Further audits should be undertaken at intervals defined by the quality risk management process to ensure the maintenance of standards and continued use of the approved supply chain.

Excipients

Excipients and excipient suppliers should be controlled appropriately based on the results of a formalised quality risk assessment in accordance with the European Commission 'Guidelines on the formalised risk assessment for ascertaining the appropriate Good Manufacturing Practice for excipients of medicinal products for human use'.

5.30 For each delivery of starting material the containers should be checked for integrity of package, including tamper evident seal where relevant, and for correspondence between the delivery note, the purchase order, the supplier's labels and approved manufacturer and supplier information maintained by the medicinal product manufacturer. The receiving checks on each delivery should be documented.

5.31 If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.

5.32 Starting materials in the storage area should be appropriately labelled (see section 13). Labels should bear at least the following information:

i. The designated name of the product and the internal code reference where applicable;

ii. A batch number given at receipt;

iii. Where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);

iv. 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.

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

5.34 Only starting materials which have been released by the Quality Control department and which are within their retest period should be used.

5.35 Manufacturers of finished products are responsible for any testing of starting materials[2] as described in the marketing authorisation dossier. They can utilise partial or full test results from the approved starting material manufacturer but must, as a minimum, perform identification testing[3] of each batch according to Annex 8.

5.36 The rationale for the outsourcing of this testing should be justified and documented and the following requirements should be fulfilled:

i. Special attention should be paid to the distribution controls (transport, wholesaling, storage and delivery) in order to maintain the quality characteristics of the starting materials and to ensure that test results remain applicable to the delivered material;
ii. The medicinal product manufacturer should perform audits, either itself or via third parties, at appropriate intervals based on risk at the site(s) carrying out the testing (including sampling) of the starting materials in order to assure compliance with Good Manufacturing Practice and with the specifications and testing methods described in the marketing authorisation dossier;
iii. The certificate of analysis provided by the starting material manufacturer/supplier should be signed by a designated person with appropriate qualifications and experience. The signature assures that each batch has been checked for compliance with the agreed product specification unless this assurance is provided separately;
iv. The medicinal product manufacturer should have appropriate experience in dealing with the starting material manufacturer (including experience via a supplier) including assessment of batches previously received and the history of compliance before reducing in-house testing. Any significant change in the manufacturing or testing processes should be considered;
v. The medicinal product manufacturer should also perform (or via a separately approved contract laboratory) a full analysis at appropriate intervals based on risk and compare the results with the material manufacturer or supplier's certificate of analysis in order to check the reliability of the latter. Should this testing identify any discrepancy then an investigation should be performed and appropriate measures taken. The acceptance of certificates of analysis from the material manufacturer or supplier should be discontinued until these measures are completed.

5.37 Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

5.38 Each dispensed material and its weight or volume should be independently checked and the check recorded.

5.39 Materials dispensed for each batch should be kept together and conspicuously labelled as such.

[2] A similar approach should apply to packaging materials as stated in section 5.45.

[3] Identity testing of starting materials should be performed according to the methods and the specifications of the relevant marketing authorisation dossier.

Processing operations: intermediate and bulk products

5.40 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.

5.41 Intermediate and bulk products should be kept under appropriate conditions.

5.42 Critical processes should be validated (see "Validation" in this Chapter).

5.43 Any necessary in-process controls and environmental controls should be carried out and recorded.

5.44 Any significant deviation from the expected yield should be recorded and investigated.

Packaging materials

5.45 The selection, qualification, approval and maintenance of suppliers of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.

5.46 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorised access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorised personnel following an approved and documented procedure.

5.47 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

5.48 Outdated or obsolete primary packaging material or printed packaging material should be destroyed, and this disposal recorded.

Packaging operations

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

5.50 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation. The line-clearance should be performed according to an appropriate check-list.

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

5.52 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the Packaging Instructions.

5.53 Containers for filling should be clean before filling. Attention should be given to avoid and remove any contaminants such as glass fragments and metal particles.

5.54 Normally, filling and sealing should be followed as quickly as possible by labelling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

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

5.56 Special care should be taken when using cut-labels and when over-printing is carried out off-line. Roll-feed labels are normally preferable to cut-labels, in helping to avoid mix-ups.

5.57 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

5.58 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

5.59 On-line control of the product during packaging should include at least checking the following:

i. General appearance of the packages;
ii. Whether the packages are complete;
iii. Whether the correct products and packaging materials are used;
iv. Whether any over-printing is correct;
v. Correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

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

5.61 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

5.62 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if un-coded printed materials are returned to stock.

Finished products

5.63 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.

5.64 The evaluation of finished products and documentation which is necessary before release of product for sale is described in Chapter 6 (Quality Control).

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

Rejected, recovered and returned materials

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

5.67 The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorised procedure after evaluation of the risks involved. Record should be kept of the reprocessing.

5.68 The recovery of all or part of earlier batches which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorised beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.

5.69 The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.

5.70 Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for re-sale, re-labelling or recovery in a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical reprocessing to recover active ingredient may be possible. Any action taken should be appropriately recorded.

Product shortage due to manufacturing constraints

5.71 The manufacturer should report to the marketing authorisation holder (MAH) any constraints in manufacturing operations which may result in abnormal restriction in the supply. This should be done in a timely manner to facilitate reporting of the restriction in supply by the MAH, to the relevant competent authorities, in accordance with its legal obligations[4].

[4]Articles 23a and 81 of Directive 2001/83/EC

Chapter 6
Quality Control

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.
Status of the document: Revision
Reasons for changes: Inclusion of a new section on technical transfer of testing methods and other items such as Out Of Specification results.
Deadline for coming into operation: 1 October 2014

Principle

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

General

6.1 Each holder of a manufacturing authorisation should have a Quality Control Department. This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.

6.2 The principal duties of the head of Quality Control are summarised in Chapter 2. The Quality Control Department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, oversee the control of the reference and/or retention samples of materials and products when applicable, ensure the correct labelling of containers of materials and products, ensure the monitoring of the stability of the products, participate in the investigation of complaints related to the quality of the product, etc. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

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

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

Good Quality Control Laboratory Practice

6.5 Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3. Laboratory equipment should not be routinely moved between high risk areas to avoid accidental cross-contamination. In particular, the microbiological laboratory should be arranged so as to minimize risk of cross-contamination.

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

Documentation

6.7 Laboratory documentation should follow the principles given in Chapter 4. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department:

i. Specifications;
ii. Procedures describing sampling, testing, records (including test worksheets and/or laboratory notebooks), recording and verifying;
iii. Procedures for and records of the calibration/qualification of instruments and maintenance of equipment;
iv. A procedure for the investigation of Out of Specification and Out Of Trend results;
v. Testing reports and/or certificates of analysis;
vi. Data from environmental (air, water and other utilities) monitoring, where required;
vii. Validation records of test methods, where applicable.

6.8 Any Quality Control documentation relating to a batch record should be retained following the principles given in chapter 4 on retention of batch documentation.

6.9 Some kinds of data (e.g. tests results, yields, environmental controls) should be recorded in a manner permitting trend evaluation. Any out of trend or out of specification data should be addressed and subject to investigation.

6.10 In addition to the information which is part of the batch documentation, other raw data such as laboratory notebooks and/or records should be retained and readily available

Sampling

6.11 The sample taking should be done and recorded in accordance with approved written procedures that describe:

i. The method of sampling;
ii. The equipment to be used;
iii. The amount of the sample to be taken;
iv. Instructions for any required sub-division of the sample;
v. The type and condition of the sample container to be used;

vi. The identification of containers sampled;
vii. Any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
viii. The storage conditions;
ix. Instructions for the cleaning and storage of sampling equipment

6.12 Samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process). The sampling plan used should be appropriately justified and based on a risk management approach.

6.13 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn. They should be managed in a manner to minimize the risk of mix-up and to protect the samples from adverse storage conditions.

6.14 Further guidance on reference and retention samples is given in Annex 19.

Testing

6.15 Testing methods should be validated. A laboratory that is using a testing method and which did not perform the original validation, should verify the appropriateness of the testing method. All testing operations described in the marketing authorisation or technical dossier should be carried out according to the approved methods.

6.16 The results obtained should be recorded. Results of parameters identified as quality attribute or as critical should be trended and checked to make sure that they are consistent with each other. Any calculations should be critically examined.

6.17 The tests performed should be recorded and the records should include at least the following data:

i. Name of the material or product and, where applicable, dosage form;
ii. Batch number and, where appropriate, the manufacturer and/or supplier;
iii. References to the relevant specifications and testing procedures;
iv. Test results, including observations and calculations, and reference to any certificates of analysis;
v. Dates of testing;
vi. Initials of the persons who performed the testing;
vii. Initials of the persons who verified the testing and the calculations, where appropriate;
viii. A clear statement of approval or rejection (or other status decision) and the dated signature of the designated responsible person; ix. Reference to the equipment used

6.18 All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.

6.19 Special attention should be given to the quality of laboratory reagents, solutions, glassware, reference standards and culture media. They should be prepared and controlled in accordance with written procedures. The level of controls should be commensurate to their use and to the available stability data.

6.20 Reference standards should be established as suitable for their intended use. Their qualification and certification as such should be clearly stated and documented. Whenever compendial reference standards from an officially recognised source exist, these should preferably be used as primary reference standards unless fully justified (the use of secondary standards is permitted once their traceability to primary standards has been demonstrated and is documented). These compendial materials should be used for the purpose described in the appropiate monograph unless otherwise authorised by the National Competent Authority.

6.21 Laboratory reagents, solutions, reference standards and culture media should be marked with the preparation and opening date and the signature of the person who prepared them. The expiry date of reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardisation and the last current factor should be indicated.

6.22 Where necessary, the date of receipt of any substance used for testing operations (e.g. reagents, solutions and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

6.23 Culture media should be prepared in accordance with the media manufacturer's requirements unless scientifically justified. The performance of all culture media should be verified prior to use.

6.24 Used microbiological media and strains should be decontaminated according to a standard procedure and disposed of in a manner to prevent the cross-contamination and retention of residues. The in-use shelf life of microbiological media should be established, documented and scientifically justified.

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

On-going stability programme

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

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

6.28 This mainly applies to the medicinal product in the package in which it is sold, but consideration should also be given to the inclusion in the programme of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied under

ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored on an on-going basis. However, when relevant, the stability of reconstituted product can also be monitored.

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

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

i. Number of batch(es) per strength and different batch sizes, if applicable;
ii. Relevant physical, chemical, microbiological and biological test methods;
iii. Acceptance criteria;
iv. Reference to test methods;
v. Description of the container closure system(s);
vi. Testing intervals (time points);
vii. Description of the conditions of storage (standardised ICH/VICH conditions for long term testing, consistent with the product labelling, should be used);
viii. Other applicable parameters specific to the medicinal product.

6.31 The protocol for the on-going stability programme can be different from that of the initial longterm stability study as submitted in the marketing authorisation dossier provided that this is justified and documented in the protocol (for example the frequency of testing, or when updating to ICH/VICH recommendations).

6.32 The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none are produced during that year). For products where on-going stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk-benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.

6.33 In certain situations, additional batches should be included in the on-going stability programme. For example, an on-going stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing or recovery operation should also be considered for inclusion.

6.34 Results of on-going stability studies should be made available to key personnel and, in particular, to the Qualified Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned. Results of on-going stability studies should be available at the site of manufacture for review by the competent authority.

6.35 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, affecting product batches released on the market should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with Chapter 8 of the GMP Guide and in consultation with the relevant competent authorities.

6.36 A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

Technical transfer of testing methods

6.37 Prior to transferring a test method, the transferring site should verify that the test method(s) comply with those as described in the Marketing Authorisation or the relevant technical dossier. The original validation of the test method(s) should be reviewed to ensure compliance with current ICH/VICH requirements. A gap analysis should be performed and documented to identify any supplementary validation that should be performed, prior to commencing the technical transfer process.

6.38 The transfer of testing methods from one laboratory (transferring laboratory) to another laboratory (receiving laboratory) should be described in a detailed protocol.

6.39 The transfer protocol should include, but not be limited to, the following parameters:

i. Identification of the testing to be performed and the relevant test method(s) undergoing transfer;
ii. Identification of the additional training requirements;
iii. Identification of standards and samples to be tested;
iv. Identification of any special transport and storage conditions of test items;
v. The acceptance criteria which should be based upon the current validation study of the methodology and with respect to ICH/VICH requirements.

6.40 Deviations from the protocol should be investigated prior to closure of the technical transfer process. The technical transfer report should document the comparative outcome of the process and should identify areas requiring further test method revalidation, if applicable.

6.41 Where appropriate, specific requirements described in others European Guidelines, should be addressed for the transfer of particular testing methods (e.g Near Infrared Spectroscopy).

Chapter 7
Outsourced Activities

Legal basis for publishing the detailed guidelines: Article 47 of Directive 2001/83/EC on the Community code relating to medicinal products for human use and Article 51 of Directive 2001/82/EC on the Community code relating to veterinary medicinal products. This document provides guidance for the interpretation of the principles and guidelines of good manufacturing practice (GMP) for medicinal products as laid down in Directive 2003/94/EC for medicinal products for human use and Directive 91/412/EEC for veterinary use.
Status of the document: revision 1
Reasons for changes: In view of the ICH Q10 guideline on the Pharmaceutical Quality System, Chapter 7 of the GMP Guide has been revised in order to provide updated guidance on outsourced GMP regulated activities beyond the current scope of contract manufacture and analysis operations. The title of the Chapter has been changed to reflect this.
Deadline for coming into operation: 31 January 2013

Principle

Any activity covered by the GMP Guide that is outsourced should be appropriately defined, agreed and controlled in order to avoid misunderstandings which could result in a product or operation of unsatisfactory quality. There must be a written Contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party. The Quality Management System of the Contract Giver must clearly state the way that the Qualified Person certifying each batch of product for release exercises his full responsibility.
Note: *This Chapter deals with the responsibilities of manufacturers towards the Competent Authorities of the Member States with respect to the granting of marketing and manufacturing authorizations. It is not intended in any way to affect the respective liability of Contract Acceptors and Contract Givers to consumers; this is governed by other provisions of Community and national law.*

General

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

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

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

The Contract Giver

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

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

7.6 The Contract Giver should provide the Contract Acceptor with all the information and knowledge necessary to carry out the contracted operations correctly in accordance with regulations in force, and the Marketing Authorisation for the product concerned. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products.

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

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

The Contract Acceptor

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

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

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

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

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

The Contract

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

7.15 The Contract should describe clearly who undertakes each step of the outsourced activity, e.g. knowledge management, technology transfer, supply chain, subcontracting, quality and purchasing of materials, testing and releasing materials, undertaking production and quality controls (including in-process controls, sampling and analysis).

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

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

Chapter 8
Complaints, Quality Defects and Product Recalls

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

Status of the document: Revision

Reasons for changes: Extensive changes have been made to this Chapter which now reflect that Quality Risk Management principles should be applied when investigating quality defects or complaints and when making decisions in relation to product recalls or other risk-mitigating actions. It emphasises the need for the cause(s) of quality defects or complaints to be investigated and determined, and that appropriate preventative actions are put in place to guard against a recurrence of the issue and clarifies expectations and responsibilities in relation to the reporting of quality defects to the Competent Authorities.

Deadline for coming into operation: 1 March 2015.

Principle

In order to protect public and animal health, a system and appropriate procedures should be in place to record, assess, investigate and review complaints including potential quality defects, and if necessary, to effectively and promptly recall medicinal products for human or veterinary use and investigational medicinal products from the distribution network. Quality Risk Management principles should be applied to the investigation and assessment of quality defects and to the decision-making process in relation to product recalls corrective and preventative actions and other risk-reducing actions. Guidance in relation to these principles is provided in Chapter 1.

All concerned competent authorities should be informed in a timely manner in case of a confirmed quality defect (faulty manufacture, product deterioration, detection of falsification, non-compliance with the marketing authorisation or product specification file, or any other serious quality problems) with a medicinal or investigational medicinal product which may result in the recall of the product or an abnormal restriction in the supply. In situations where product on the market is found to be non-compliant with the marketing authorisation, there is no requirement to notify concerned competent authorities provided the degree of non-compliance satisfies the Annex 16 restrictions regarding the handling of unplanned deviations.

In case of outsourced activities, a contract should describe the role and responsibilities of the manufacturer, the marketing authorisation holder and/or sponsor and any other relevant third parties in relation to assessment, decision-making, and dissemination of information and

implementation of risk-reducing actions relating to a defective product. Guidance in relation to contracts is provided in Chapter 7. Such contracts should also address how to contact those responsible at each party for the management of quality defect and recall issues.

Personnel and Organisation

8.1 Appropriately trained and experienced personnel should be responsible for managing complaint and quality defect investigations and for deciding the measures to be taken to manage any potential risk(s) presented by those issues, including recalls. These persons should be independent of the sales and marketing organisation, unless otherwise justified. If these persons do not include the Qualified Person involved in the certification for release of the concerned batch or batches, the latter should be made formally aware of any investigations, any risk-reducing actions and any recall operations, in a timely manner.

8.2 Sufficient trained personnel and resources should be made available for the handling, assessment, investigation and review of complaints and quality defects and for implementing any risk-reducing actions. Sufficient trained personnel and resources should also be available for the management of interactions with competent authorities.

8.3 The use of inter-disciplinary teams should be considered, including appropriately trained Quality Management personnel.

8.4 In situations in which complaint and quality defect handling is managed centrally within an organisation, the relative roles and responsibilities of the concerned parties should be documented. Central management should not, however, result in delays in the investigation and management of the issue.

Procedures for handling and investigating complaints including possible quality defects

8.5 There should be written procedures describing the actions to be taken upon receipt of a complaint. All complaints should be documented and assessed to establish if they represent a potential quality defect or other issue.

8.6 Special attention should be given to establishing whether a complaint or suspected quality defect relates to falsification.

8.7 As not all complaints received by a company may represent actual quality defects, complaints which do not indicate a potential quality defect should be documented appropriately and communicated to the relevant group or person responsible for the investigation and management of complaints of that nature, such as suspected adverse events.

8.8 There should be procedures in place to facilitate a request to investigate the quality of a batch of a medicinal product in order to support an investigation into a reported suspected adverse event.

8.9 When a quality defect investigation is initiated, procedures should be in place to address at least the following:

i. The description of the reported quality defect.

ii. The determination of the extent of the quality defect. The checking or testing of reference and/or retention samples should be considered as part of this, and in certain cases, a review of the batch production record, the batch certification

record and the batch distribution records (especially for temperature-sensitive products) should be performed.

iii. The need to request a sample, or the return, of the defective product from the complainant and, where a sample is provided, the need for an appropriate evaluation to be carried out.

iv. The assessment of the risk(s) posed by the quality defect, based on the severity and extent of the quality defect.

v. The decision-making process that is to be used concerning the potential need for risk reducing actions to be taken in the distribution network, such as batch or product recalls, or other actions.

vi. The assessment of the impact that any recall action may have on the availability of the medicinal product to patients/animals in any affected market, and the need to notify the relevant authorities of such impact.

vii. The internal and external communications that should be made in relation to a quality defect and its investigation.

viii. The identification of the potential root cause(s) of the quality defect.

ix. The need for appropriate Corrective and Preventative Actions (CAPAs) to be identified and implemented for the issue, and for the assessment of the effectiveness of those CAPAs.

Investigation and Decision-making

8.10 The information reported in relation to possible quality defects should be recorded, including all the original details. The validity and extent of all reported quality defects should be documented and assessed in accordance with Quality Risk Management principles in order to support decisions regarding the degree of investigation and action taken.

8.11 If a quality defect is discovered or suspected in a batch, consideration should be given to checking other batches and in some cases other products, in order to determine whether they are also affected. In particular, other batches which may contain portions of the defective batch or defective components should be investigated.

8.12 Quality defect investigations should include a review of previous quality defect reports or any other relevant information for any indication of specific or recurring problems requiring attention and possibly further regulatory action.

8.13 The decisions that are made during and following quality defect investigations should reflect the level of risk that is presented by the quality defect as well as the seriousness of any non-compliance with respect to the requirements of the marketing authorisation/product specification file or GMP. Such decisions should be timely to ensure that patient and animal safety is maintained, in a way that is commensurate with the level of risk that is presented by those issues.

8.14 As comprehensive information on the nature and extent of the quality defect may not always be available at the early stages of an investigation, the decision-making processes should still ensure that appropriate risk-reducing actions are taken at an appropriate timepoint during such investigations. All the decisions and measures taken as a result of a quality defect should be documented.

8.15 Quality defects should be reported in a timely manner by the manufacturer to the marketing authorisation holder/sponsor and all concerned Competent Authorities in cases where the quality defect may result in the recall of the product or in an abnormal restriction in the supply of the product.

Root Cause Analysis and Corrective and Preventative Actions

8.16 An appropriate level of root cause analysis work should be applied during the investigation of quality defects. In cases where the true root cause(s) of the quality defect cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those.

8.17 Where human error is suspected or identified as the cause of a quality defect, this should be formally justified and care should be exercised so as to ensure that process, procedural or system-based errors or problems are not overlooked, if present.

8.18 Appropriate CAPAs should be identified and taken in response to a quality defect. The effectiveness of such actions should be monitored and assessed.

8.19 Quality defect records should be reviewed and trend analyses should be performed regularly for any indication of specific or recurring problems requiring attention.

Product Recalls and other potential risk-reducing actions

8.20 There should be established written procedures, regularly reviewed and updated when necessary, in order to undertake any recall activity or implement any other risk-reducing actions.

8.21 After a product has been placed on the market, any retrieval of it from the distribution network as a result of a quality defect should be regarded and managed as a recall. (This provision does not apply to the retrieval (or return) of samples of the product from the distribution network to facilitate an investigation into a quality defect issue/report.)

8.22 Recall operations should be capable of being initiated promptly and at any time. In certain cases recall operations may need to be initiated to protect public or animal health prior to establishing the root cause(s) and full extent of the quality defect

8.23 The batch/product distribution records should be readily available to the persons responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples.

8.24 In the case of investigational medicinal products, all trial sites should be identified and the countries of destination should be indicated. In the case of an investigational medicinal product for which a marketing authorisation has been issued, the manufacturer of the investigational medicinal product should, in cooperation with the sponsor, inform the marketing authorisation holder of any quality defect that could be related to the authorised medicinal product. The sponsor should implement a procedure for the rapid unblinding of blinded products, where this is necessary for a prompt recall. The sponsor should ensure that the procedure discloses the identity of the blinded product only in so far as is necessary.

8.25 Consideration should be given following consultation with the concerned Competent Authorities, as to how far into the distribution network a recall action should extend, taking into account the potential risk to public or animal health and any impact that the proposed recall action may have. The Competent Authorities should also be informed in situations in which no recall action is being proposed for a defective batch because the batch has expired (such as with short shelf-life products.)

8.26 All concerned Competent Authorities should be informed in advance in cases where products are intended to be recalled. For very serious issues (i.e. those with the potential to seriously impact upon patient or animal health), rapid risk-reducing actions (such as a product recall) may have to be taken in advance of notifying the Competent Authorities. Wherever possible, attempts should be made to agree these in advance of their execution with the concerned Competent Authorities

8.27 It should also be considered whether the proposed recall action may affect different markets in different ways, and if this is the case, appropriate market-specific risk-reducing actions should be developed and discussed with the concerned competent authorities. Taking account of its therapeutic use the risk of shortage of a medicinal product which has no authorised alternative should be considered before deciding on a risk-reducing action such as a recall. Any decisions not to execute a risk-reducing action which would otherwise be required should be agreed with the competent authority in advance.

8.28 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate. A formal disposition of all recalled batches should be made and documented. The rationale for any decision to rework recalled products should be documented and discussed with the relevant competent authority. The extent of shelf life remaining for any reworked batches that are being considered for placement onto the market should also be considered.

8.29 The progress of the recall process should be recorded until closure and a final report issued, including a reconciliation between the delivered and recovered quantities of the concerned products/batches.

8.30 The effectiveness of the arrangements in place for recalls should be periodically evaluated to confirm that they remain robust and fit for use. Such evaluations should extend to both within office-hour situations as well as out-of-office hour situations and, when performing such evaluations, consideration should be given as to whether mock-recall actions should be performed. This evaluation should be documented and justified.

8.31 In addition to recalls, there are other potential risk-reducing actions that may be considered in order to manage the risks presented by quality defects. Such actions may include the issuance of cautionary communications to healthcare professionals in relation to their use of a batch that is potentially defective. These should be considered on a case by-case basis and discussed with the concerned competent authorities.

CHAPTER 9
SELF INSPECTION

Principle

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

9.1 Personnel matters, premises, equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self inspection, should be examined at intervals following a pre-arranged programme in order to verify their conformity with the principles of Quality Assurance.

9.2 Self inspections should be conducted in an independent and detailed way by designated competent person(s) from the company. Independent audits by external experts may also be useful.

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

Annex 1
Manufacture of Sterile Medicinal Products (corrected version)

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 procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test. Note: This guidance does not lay down detailed methods for determining the microbiological and particulate cleanliness of air, surfaces etc. Reference should be made to other documents such as the EN/ISO Standards.

General

1. The manufacture of sterile products should be carried out in clean areas entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should 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 should 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 should 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 should 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 should 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 should 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, this 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 should be classified in accordance with EN ISO 14644-1. Classification should 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 m3 equal to or greater than the tabulated size			
	At rest		**In operation**	
Grade	**0.5 µm**	**5.0µm**	**0.5 µm**	**5.0µm**
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**	**Not defined**	**Not defined**

5. For classification purposes in Grade A zones, a minimum sample volume of 1m 3 should 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 & 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 should 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 should 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 should 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 should be undertaken prior to exposure to the risk. Monitoring during simulated operations should also be performed. The Grade A

zone should 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 should be determined by the effectiveness of the segregation between the adjacent Grade A and B zones. The Grade B zone should 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 should 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 should 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 should 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 should 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” should be attained.
16. Other characteristics such as temperature and relative humidity depend on the product and nature of the operations carried out. These parameters should not interfere with the defined cleanliness standard.
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 should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should 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/m3**	**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**	**< 1**	**< 1**
B	**10**	**5**	**5**	**5**
C	**100**	**50**	**25**	**-**
D	**200**	**100**	**50**	**-**

Notes

(a) These are average values.

(b) Individual settle plates may be exposed for less than 4 hours.

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

Isolator technology

21. 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 should 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 should be controlled and for aseptic processing it should be at least grade D.
24. Isolators should be introduced only after appropriate validation. Validation should 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 should be carried out routinely and should 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 should 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 should be installed in at least a grade D environment.
27. Because of this special technology particular attention should be paid to, at least the following:
    - equipment design and qualification
    - validation and reproducibility of cleaning-in-place and sterilisation-in-place
    - background clean room environment in which the equipment is located
    - operator training and clothing
    - interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

Terminally sterilised products

28. Preparation of components and most products should 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, (for example, 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 should be carried out in a grade C environment.
29. Filling of products for terminal sterilisation should 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 should be

done in a grade A zone with at least a grade C background. Preparation and filling of ointments, creams, suspensions and emulsions should generally be carried out in a grade C environment before terminal sterilisation.

Aseptic preparation

31. Components after washing should 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, should be done in a grade A environment with grade B background.
32. Preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not filtered, the preparation of materials and products should be done in a grade A environment with a grade B background.
33. Handling and filling of aseptically prepared products should 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 should 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 should 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 should be present in clean areas; this is particularly important during aseptic processing. Inspections and controls should be conducted outside the clean areas as far as possible.
37. All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products. This training should 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 should 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 should 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 should 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 should be decided by a designated competent person.
40. Wristwatches, make-up and jewellery should not be worn in clean areas.
41. Changing and washing should 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 should be appropriate for the process and the grade of the working area. It should be worn in such a way 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 should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.
    - Grade C: Hair and where relevant beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.
    - Grade A/B: Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear should be worn. Trouser-legs should be tucked inside the footwear and garment sleeves into the gloves. The protective clothing should shed virtually no fibres or particulate matter and retain particles shed by the body.

44. Outdoor clothing should 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 should be provided at each work session. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least for every working session.

45. Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. These operations should 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 should 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 should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to avoid those uncleanable recesses; sliding doors may be undesirable for this reason.

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

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

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

51. Changing rooms should 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 should be flushed effectively with filtered air. The final stage of the changing room should, 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 should be provided only in the first stage of the changing rooms.
52. Both airlock doors should not be opened simultaneously. An interlocking system or a visual and/or audible warning system should be operated to prevent the opening of more than one door at a time.
53. A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10 - 15 pascals (guidance values). Particular attention should 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 should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should 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 should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.

Equipment

56. A conveyor belt should 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 should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilisation is required, it should be carried out, wherever possible, after complete reassembly.
58. When equipment maintenance has been carried out within the clean area, the area should 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 should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Water for injections should 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 should be subject to validation and planned maintenance; their return to use should be approved.

Sanitation

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

62. Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilised. Disinfectants and detergents used in Grades A and B areas should 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 should be taken during all processing stages including the stages before sterilisation.

65. Preparations of microbiological origin should 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 should include a process simulation test using a nutrient medium (media fill).Selection of the nutrient medium should 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 should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. It should also take into account various interventions known to occur during normal production as well as worst-case situations.

68. Process simulation tests should 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 should be repeated twice a year per shift and process.

69. The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth and the following should apply:

- When filling fewer than 5000 units, no contaminated units should be detected.
- When filling 5,000 to 10,000 units:

(a) One (1) contaminated unit should 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 10,000 units:
  (a) One (1) contaminated unit should 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 should be investigated. Investigation of gross failures should include the potential impact on the sterility assurance of batches manufactured since the last successful media fill.
71. Care should be taken that any validation does not compromise the processes.
72. Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins. Records should 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 should be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.
74. Microbiological contamination of starting materials should be minimal. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.
75. Containers and materials liable to generate fibres should be minimised in clean areas.
76. Where appropriate, measures should be taken to minimize the particulate contamination of the end product.
77. Components, containers and equipment should 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 should 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 should be minimised. There should be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.
80. The bioburden should be monitored before sterilisation. There should be working limits on contamination immediately before sterilisation, which are related to the efficiency of the method to be used. Bioburden assay should 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 should be performed on each batch and considered as an in-process test. Where appropriate the level of endotoxins should be monitored. All

solutions, in particular large volume infusion fluids, should 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 should 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 should be passed through micro-organism retentive filters.

82. The efficacy of any new procedure should 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 should be validated. Particular attention should 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 should be demonstrated by physical measurements and by biological indicators where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

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

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

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

88. There should 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 should 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 should be available for each sterilisation run. They should be approved as part of the batch release procedure.

Sterilisation by heat

90. Each heat sterilisation cycle should 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 should 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 should 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 should be taken against contamination of a sterilised load during cooling. Any cooling fluid or gas in contact with the product should be sterilised unless it can be shown that any leaking container would not be approved for use.

Moist heat

94. Both temperature and pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator. The reading of the independent temperature indicator should 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 should 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, should 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 should be in contact with the sterilizing agent at the required temperature for the required time.

96. Care should 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 should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should 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 should be measured. For this purpose, dosimetry indicators which are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters should 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 should be used within the time-limit of their calibration. Dosimeter absorbances should be read within a short period after exposure to radiation.
100. Biological indicators may be used as an additional control
101. Validation procedures should ensure that the effects of variations in density of the packages are considered.
102. Materials handling procedures should prevent mix-up between irradiated and nonirradiated materials. Radiation sensitive colour disks should 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 should be administered within a predetermined time span.

Sterilisation with ethylene oxide

104. This method should only be used when no other method is practicable. During process validation it should 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 should 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 should be brought into equilibrium with the humidity and temperature required by the process. The time required for this should be balanced against the opposing need to minimize the time before sterilisation.
107. Each sterilisation cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.
108. For each sterilisation cycle, records should 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 should be recorded throughout the cycle on a chart. The record(s) should form part of the batch record.
109. After sterilisation, the load should be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process should 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 should 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 sterilization processes, a second filtration via a further sterilised micro-organism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.
112. Fibre-shedding characteristics of filters should be minimal.
113. The integrity of the sterilised filter should be verified before use and should 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 should be determined during validation and any significant differences from this during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.
114. The same filter should not be used for more than one working day unless such use has been validated.
115. The filter should 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 should be maintained under Grade A conditions at all times until the stopper is fully inserted.
117. Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should 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 should 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 should 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 should be protected by Grade A conditions up to the point of leaving the aseptic processing area, and thereafter stoppered vials should be protected with a Grade A air supply until the cap has been crimped.
121. Vials with missing or displaced stoppers should be rejected prior to capping. Where human intervention is required at the capping station, appropriate technology should

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 should be tested for maintenance of that vacuum after an appropriate, pre-determined period.

124. Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should 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 should be validated and the performance of the equipment checked at intervals. Results should be recorded.

Quality control

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

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

127. Samples taken for sterility testing should be representative of the whole of the batch, but should 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 should 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 should be given to taking samples from the potentially coolest part of the load.

Annex 2
Manufacture of Biological active substances and Medicinal Products for Human Use

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

Status of the document: revision 2

Reasons for changes: Annex 2 of the GMP Guide has been revised as a consequence of the adoption of the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products pursuant to Article 5 of Regulation (EC) 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004[1]

Deadline for coming into operation: 26 June 2018

[1] Regulation (EC) No 1394 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 324, 10.12.2007, p.121

Scope

The methods employed in the manufacture of biological active substances and biological medicinal products for human use ('biological active substances and medicinal products') are a critical factor in shaping the appropriate regulatory control. Biological active substances and medicinal products can be defined therefore largely by reference to their method of manufacture. This annex provides guidance on the full range of active substances and medicinal products defined as biological, with the exception of Advanced Therapy Medicinal Products ("ATMPs"), as defined in Article 1(1) of Regulation (EC) No 1394/2007[1]. The ATMPs are not covered by the present guideline. Manufacturers of ATMPs should refer to the Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products referred to in Article 5 of the above quoted Regulation.

This annex is divided into two main parts:

(a) Part A contains supplementary guidance on the manufacture of biological active substances and medicinal products, from control over seed lots and cell banks through to finishing activities, and testing.

(b) Part B contains further guidance on selected types of biological active substances and medicinal products. This annex, along with several other annexes of the Guide to GMP in EudraLex Volume 4, provides guidance which supplements that in Part I and in Part II of that Guide.

There are two aspects to the scope of this annex:

(a) Stage of manufacture - for biological active substances to the point immediately prior to their being rendered sterile, the primary guidance source is Part II. Guidance for the subsequent manufacturing steps of biological products are covered in Part I.

(b) Type of product - this annex provides guidance on the full range of medicinal products defined as biological, with the exception of ATMPs.

These two aspects are shown in Table 1, it should be noted that this table is illustrative only and is not meant to describe the precise scope. It should also be understood that in line with the corresponding table in Part II of EudraLex, Volume 4, the level of GMP increases in detail from early to later steps in the manufacture of biological active substances but GMP principles should always be adhered to. The inclusion of some early steps of manufacture within the scope of this Annex does not imply that those steps will be routinely subject to inspection by the authorities.

Antibiotics are not defined as biological medicinal products, however where biological stages of manufacture occur, guidance in this Annex may be used.

Guidance for medicinal products derived from fractionated human blood or plasma is covered in Annex 14 of EudraLex, Volume 4, and for non-transgenic plant products in Annex 7.

[1] Regulation (EC) No 1394 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, OJ L 324, 10.12.2007, p.121

In certain cases, other legislation is applicable to the starting materials. For example,

(a) Tissue and cells used as starting materials for medicinal products: Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells,[2] and Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells[3] cover only their donation, procurement and testing. Such tissues and cells may provide the active substances for some biological medicinal product within the scope of this annex at which point GMP and other medicinal product legislation requirements apply.

(b) Blood or blood components used as starting materials for medicinal products: Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC4 and its Commission Directives provides the technical requirements 5 for the selection of donors and the collection and testing of blood and blood components.

Additionally, the manufacture and control of genetically modified organisms needs to comply with local and national requirements. In accordance with Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms, 6 appropriate containment and other protective measures shall be established and maintained in facilities where any genetically modified micro-organism are handled. Advice should be obtained according to national legislation in order to establish and maintain the appropriate Biological Safety Level. There should be no conflicts with GMP requirements.

2 OJ L 102, 7.4.2004, p. 48.

Table 1. Illustrative guide to manufacturing activities within the scope of Annex 2.

Type and source of material	Example product	Application of this guide to manufacturing steps shown in grey			
1. Animal or plant sources: non-transgenic	Heparins, insulin, enzymes, proteins, allergen extract immunosera	Collection of plant, organ, animal material or fluid[7]	Cutting, mixing, and /or initial processing	Isolation and purification	Formulation, filling
2. Virus or bacteria/ fermentation/ cell culture	Viral or bacterial vaccines; enzymes, proteins	Establishment & maintenance of MCB[8], WCB, MVS, WVS	Cell culture and/or fermentation	Inactivation when applicable, isolation and purification	Formulation, filling
3. Biotechnology - fermentation/ cell culture	Recombinant products, MAb, allergens, vaccines	Establishment & maintenance of MCB and WCB, MSL, WSL	Cell culture and/or fermentation	Isolation, purification, modification	Formulation, filling
4. Animal sources: transgenic	Recombinant proteins,	Master and working transgenic bank	Collection, cutting, mixing, and / or initial processing	Isolation, purification, modification	Formulation, filling
5. Plant sources: transgenic	Recombinant proteins, vaccines, allergen	Master and working transgenic bank	Growing, harvesting[9]	Initial extraction, isolation, purification, modification	Formulation, filling
6.Human sources	Urine derived enzymes, hormones	Collection of fluid[10]	Mixing, and/or initial processing	Isolation and purification	Formulation, filling
7. Human sources	Products from cells tissues	Donation, procurement and testing of starting tissue / cells[11]	Initial processing, isolation and purification.	Cell isolation, culture, purification, combination with noncellular components	Formulation, combination, filling

3 OJ L 102, 7.4.2004, p. 48.
4 OJ L 38, 9.2.2006, p. 40.
5 OJ L 33, 8.2.2003, p.30.
6 Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components and Good Practice Guidelines for blood establishments as referenced in Directive 2016/1214, amending Directive 2005/62/EC.
7 OJ L 125,21.5.2009, p. 75.
8 See section B1 for the extent to which GMP principles apply.
9 See section on 'Seed lot and cell bank system' for the extent to which GMP applies.
10 HMPC guideline on Good Agricultural and Collection Practice - EMEA/HMPC/246816/2005.
11 Principles of GMP apply, see explanatory text in 'Scope'.
12 Human tissues and cells must comply with Directive 2004/23/EC and implementing Directives at these stages.

See Glossary for explanation of acronyms.

Principle

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

Unlike conventional medicinal products, which are manufactured using chemical and physical techniques capable of a high degree of consistency, the manufacture of biological active substances and medicinal products involves biological processes and materials, such as cultivation of cells or extraction from living organisms. These biological processes may display inherent variability, so that the range and nature of by-products may be variable. As a result, quality risk management (QRM) principles are particularly important for this class of materials and should be used to develop the control strategy across all stages of manufacture so as to minimise variability and to reduce the opportunity for contamination and cross contamination.

Since materials and processing conditions used in cultivation processes are designed to provide conditions for the growth of specific cells and microorganisms, this provides extraneous microbial contaminants the opportunity to grow. In addition, some products may be limited in their ability to withstand a wide range of purification techniques particularly those designed to inactivate or remove adventitious viral contaminants. The design of the processes, equipment, facilities, utilities, the conditions of preparation and addition of buffers and reagents, sampling and training of the operators are key considerations to minimise such contamination events.

Specifications related to products (such as those in Pharmacopoeial monographs, Marketing Authorisation (MA), and Clinical Trial Authorisation, (CTA)) will dictate whether and to what stage substances and materials can have a defined level of bioburden or need to be sterile. Similarly, manufacturing must be consistent with other specifications set out in the MA or CTA guidance (e.g. number of generations (doublings, passages) between the seed lot or cell bank). For biological

For biological materials that cannot be sterilized (e.g. by filtration), processing must be conducted aseptically to minimise the introduction of contaminants. Where they exist, CHMP guidance documents should be consulted on the validation of specific manufacturing methods, e.g. virus removal or inactivation. The application of appropriate environmental controls and monitoring and, wherever feasible, in-situ cleaning and sterilization systems together with the use of closed systems can significantly reduce the risk of accidental contamination and cross contamination.

Control usually involves biological analytical techniques, which typically have a greater variability than physico-chemical determinations. A robust manufacturing process is therefore crucial and in-process controls take on a particular importance in the manufacture of biological active substances and medicinal products.

Biological medicinal products which incorporate human tissues or cells must take into account the requirements of Directive 2004/23/EC and Commission Directive 2006/17/EC. In line with Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical

requirements for the coding, processing, preservation, storage and distribution of human tissues and cells,[12] collection and testing must be done in accordance with an appropriate quality system for which standards and specifications are defined in its Annex.

Biological active substances and medicinal products must comply with the latest version of the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy (TSE) Agents via Human and Veterinary Medicinal Products.

12 OJ L 294, 25.10.2006, p. 32.

PART A. GENERAL GUIDANCE

Personnel

1. Personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where biological active substances and products are manufactured and tested should receive training, and periodic retraining, specific to the products manufactured to their work, including any specific security measures to protect product, personnel and the environment.
2. The health status of personnel should be taken into consideration for product safety. Where necessary, personnel engaged in production, maintenance, testing and animal care (and inspections) should be vaccinated with appropriate specific vaccines and have regular health checks.
3. Any changes in the health status of personnel, which could adversely affect the quality of the product, should preclude work in the production area and appropriate records kept. Production of BCG vaccine and tuberculin products should be restricted to staff who are carefully monitored by regular checks of immunological status or chest Xray. Health monitoring of staff should be commensurate with the risk, medical advice should be sought for personnel involved with hazardous organisms.
4. Where required to minimise the opportunity for cross-contamination, restrictions on the movement of all personnel (including quality control (QC), maintenance and cleaning staff) should be controlled on the basis of QRM principles. In general, personnel should not pass from areas where exposure to live micro-organisms, genetically modified organisms, toxins or animals to areas where other products, inactivated products or different organisms are handled. If such passage is unavoidable, the contamination control measures should be based on QRM principles.
   Premises and Equipment
5. As part of the control strategy, the degree of environmental control of particulate and microbial contamination of the production premises should be adapted to the active substance, intermediate or finished product and the production step, bearing in mind the potential level of contamination of the starting materials and the risks to the product. The environmental monitoring programme should be supplemented by the inclusion of methods to detect the presence of specific microorganisms (i.e. host organism, yeast, moulds, anaerobes, etc) where indicated by the QRM process.

6. Manufacturing and storage facilities, processes and environmental classifications should be designed to prevent the extraneous contamination of products. Prevention of contamination is more appropriate than detection and removal, although contamination is likely to become evident during processes such as fermentation and cell culture. Where processes are not closed and there is therefore exposure of the product to the immediate room environment (e.g. during additions of supplements, media, buffers, gasses) control measures should be put in place, including engineering and environmental controls on the basis of QRM principles. These QRM principles should take into account the principles and guidance from the appropriate sections of Annex 1 [13] to EudraLex, Volume 4, when selecting environmental classification cascades and associated controls.
7. Dedicated production areas should be used for the handling of live cells capable of persistence in the manufacturing environment. Dedicated production area should be used for the manufacture of pathogenic organisms (i.e. Biosafety level 3 or 4).
8. Manufacture in a multi-product facility may be acceptable where the following, or equivalent (as appropriate to the product types involved) considerations and measures are part of an effective control strategy to prevent cross-contamination:
   (a) Knowledge of key characteristics of all cells, organisms and any adventitious agents (e.g. pathogenicity, detectability, persistence, susceptibility to inactivation) within the same facility.
   (b) Where production is characterised by multiple small batches from different starting materials factors such as the health status of donors and the risk of total loss of product should be taken into account when considering the acceptance of concurrent working during development of the control strategy.
   (c) Live organisms and spores are prevented from entering non-related areas or equipment by addressing all potential routes of cross-contamination and utilizing single use components and engineering measures such as closed systems.
   (d) Control measures to remove the organisms and spores before the subsequent manufacture of other products, these control measures should also take the heating, ventilation and air conditioning (HVAC) system into account. Cleaning and decontamination for the organisms and spores should be validated.
   (e) Environmental monitoring specific for the micro-organism being manufactured, where the micro-organisms are capable of persistence in the manufacturing environment and where methods are available, is conducted in adjacent areas during manufacture and after completion of cleaning and decontamination. Attention should also be given to risks arising with use of certain monitoring equipment (e.g. airborne particle monitoring) in areas handling live and/or spore forming organisms.

13 Although the title of Annex 1 refers to the manufacture of sterile medicinal products it is not the intention to force the manufacture of sterile product at a stage when a low bioburden is appropriate and authorised. Its use is because it is the only EU GMP source of guidance on all of the classified manufacturing areas including the lower grades D and C.

(f) Products, equipment, ancillary equipment (e.g. for calibration and validation) and disposable items are only moved within and removed from such areas in a manner that prevents contamination of other areas, other products and different product stages (e.g. prevent contamination of inactivated or toxoided products with non-inactivated products).

(g) Campaign-based manufacturing

9. For finishing (secondary) operations[14], the need for dedicated facilities will depend on consideration of the above together with additional considerations such as the specific needs of the biological medicinal product and on the characteristics of other products, including any non-biological products, in the same facility. Other control measures for finishing operations may include the need for specific addition sequences, mixing speeds, time and temperature controls, limits on exposure to light and containment and cleaning procedures in the event of spillages.

10. The measures and procedures necessary for containment (i.e., for environment and operator safety) should not conflict with those for product quality.

11. Air handling units should be designed, constructed and maintained to minimise the risk of cross-contamination between different manufacturing areas and may need to be specific for an area. Consideration, based on QRM principles, should be given to the use of single pass air systems.

12. Positive pressure areas should be used to process sterile products but negative pressure in specific areas at the point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or safety cabinets are used for aseptic processing of materials with particular risks (e.g. pathogens) they should be surrounded by a positive pressure clean zone of appropriate grade. These pressure cascades should be clearly defined and continuously monitored with appropriate alarm settings.

13. Equipment used during handling of live organisms and cells, including those for sampling, should be designed to prevent any contamination during processing.

14. Primary containment **15** should be designed and periodically tested to ensure the prevention of escape of biological agents into the immediate working environment.

15. The use of 'clean in place' and ‘steam in place’ (‘sterilisation in place’) systems should be used where possible. Valves on fermentation vessels should be completely steam sterilisable.

16. Air vent filters should be hydrophobic and validated for their scheduled life span with integrity testing at appropriate intervals based on appropriate QRM principles.

17. Drainage systems must be designed so that effluents can be effectively neutralised or decontaminated to minimise the risk of cross-contamination. Local regulation must be complied with to minimise the risk of contamination of the external environment according to the risk associated with the bio hazardous nature of waste materials.

14 Formulation, filling and packaging

15 See main GMP Glossary on ‘Containment’

18. Due to the variability of biological products or manufacturing processes, relevant/critical raw materials (such as culture media and buffers) have to be measured or weighed during the production process. In these cases, small stocks of these raw materials may be kept in the production area for a specified duration based on defined criteria such as for the duration of manufacture of the batch or of the campaign.

Animals

19. A wide range of animal species are used in the manufacture of a number of biological medicinal products. These can be divided into 2 broad types of sources:
    (a) Live groups, herds, flocks: examples include polio vaccine (monkeys), immunosera to snake venoms and tetanus (horses, sheep and goats), allergens (cats), rabies vaccine (rabbits, mice and hamsters), transgenic products (goats, cattle).
    (b) Animal materials derived post-mortem and from establishments such as abattoirs: examples include abattoir sources for enzymes, anticoagulants and hormones (sheep and pigs).
    In addition, animals may also be used in quality control either in generic assays, e.g. pyrogenicity, or specific potency assays, e.g. pertussis vaccine (mice), pyrogenicity (rabbits), BCG vaccine (guinea-pigs).
20. In addition to compliance with TSE regulations, other adventitious agents that are of concern (zoonotic diseases, diseases of source animals) should be monitored by an ongoing health programme and recorded. Specialist advice should be obtained in establishing such programmes. Instances of ill-health occurring in the source/donor animals should be investigated with respect to their suitability and the suitability of in contact animals for continued use (in manufacture, as sources of starting and raw materials, in quality control and safety testing), the decisions must be documented. A look-back procedure should be in place which informs the decision-making process on the continued suitability of the biological active substance or medicinal product in which the animal sourced starting or raw materials have been used or incorporated. This decision-making process may include the re-testing of retained samples from previous collections from the same donor animal (where applicable) to establish the last negative donation. The withdrawal period of therapeutic agents used to treat source/donor animals must be documented and used to determine the removal of those animals from the programme for defined periods.
21. 21. Particular care should be taken to prevent and monitor infections in the source/donor animals. Measures should include the sourcing, facilities, husbandry, biosecurity procedures, testing regimes, control of bedding and feed materials. This is of special relevance to specified pathogen free animals where Ph. Eur. monograph requirements must be met. Housing and health monitoring should be defined for other categories of animals (e.g. healthy flocks or herds).
22. For products manufactured from transgenic animals, traceability should be maintained in the creation of such animals from the source animals.

23. Note should be taken of Directive 2010/63/EU on the protection of animals used for scientific purposes[16]. Housing for animals used in production and control of biological active substances and medicinal products should be separated from production and control areas.

24. For different animal species, key criteria should be defined, monitored, and recorded. These may include age, weight and health status of the animals.

25. Animals, biological agents, and tests carried out should be the subject of an identification system to prevent any risk of confusion and to control all identified hazards. Documentation

26. Starting and raw materials may need additional documentation on the source, origin, distribution chain, method of manufacture, and controls applied, to assure an appropriate level of control including their microbiological quality.

27. Some product types may require specific definition of what materials constitutes a batch, particularly cells. For autologous and donor-matched situations, the manufactured product should be viewed as a batch.

28. Where human cell or tissue donors are used full traceability is required from starting and raw materials, including all substances coming into contact with the cells or tissues through to confirmation of the receipt of the products at the point of use whilst maintaining the privacy of individuals and confidentiality of health related information. Traceability records must be retained for 30 years after the expiry date of the medicinal product. Particular care should be taken to maintain the traceability of medicinal products for special use cases, such as donor-matched cells. Directives 2002/98/EC and Commission Directive 2005/61/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events[17] apply to blood components when they are used as starting or raw materials in the manufacturing process of medicinal products.

16 Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes, OJ L 276, 10.10.2010, p.33

17 OJ L 256, 1.10.2005, p. 32.

Production

29. Given the variability inherent in many biological active substances and medicinal products, steps to increase process robustness thereby reducing process variability and enhancing reproducibility at the different stages of the product lifecycle such as process design should be reassessed during Product Quality Reviews.

30. Since cultivation conditions, media and reagents are designed to promote the growth of cells or microbial organisms, typically in an axenic state, particular attention should be paid in the control strategy to ensure there are robust steps that prevent or minimise the occurrence of unwanted bioburden and associated metabolites and endotoxins. For medicinal products from cells and tissues where production batches are frequently small the risk of cross-contamination between cell preparations from different donors with various health status should be controlled under defined procedures and requirements.

Starting and raw materials

31. The source, origin and suitability of biological starting and raw materials (e.g. cryoprotectants, feeder cells, reagents, culture media, buffers, serum, enzymes, cytokines, growth factors) should 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, the risk of using a potentially failed material and its potential impact on other batches should be clearly understood and assessed under the principles of QRM. In such cases, release of a finished product is conditional on satisfactory results of these tests. The identification of all starting materials should be in compliance with the requirements appropriate to its stage of manufacture. For biological medicinal products further guidance can be found in Part I and Annex 8 and for biological active substances in Part II.

32. The risk of contamination of starting and raw materials during their passage along the supply chain must be assessed, with particular emphasis on TSE. Materials that come into direct contact with manufacturing equipment or the product (such as media used in media fill experiments and lubricants that may contact the product) must also be taken into account.

33. Given that the risks from the introduction of contamination and the consequences to the finished product is the same irrespective of the stage of manufacture, establishment of a control strategy to protect the product and the preparation of solutions, buffers and other additions should be based on the principles and guidance contained in the appropriate sections of Annex 1. The controls required for the quality of starting and raw materials and on the aseptic manufacturing process assume greater importance, particularly for products in respect of which final sterilisation is not possible. Where an MA or CTA provides for an allowable type and level of bioburden, for example at active substance stage, the control strategy should address the means by which this is maintained within the specified limits.

34. Where sterilization of starting and raw materials is required, it should be carried out where possible by heat. Where necessary, other appropriate methods may also be used for inactivation of biological materials (e.g. irradiation and filtration).

35. Reduction in bioburden associated with procurement of living tissues and cells may require the use of other measures such as antibiotics at early manufacturing stages. This should be avoided, but where it is necessary their use should be justified, they should be removed from the manufacturing process at the stage specified in the MA or CTA.

36. The donation, procurement and testing of human tissues and cells used as starting or raw materials should be in accordance with Directive 2004/23/EC.[18] Traceability for human tissues and cells used as starting materials for biological medicinal products should be maintained from the donor to the batch of a finished medicinal product. Appropriate arrangements should be made between the manufacturer and the supplier of tissues and cells regarding the transfer of health donor information that may become available after the supply of the starting material and which may have an impact on the quality or safety of the medicinal product manufactured there from.

    (a) Their procurement, donation and testing in the EU is regulated under Directive 2004/23/EC and its implementing Commission directives. Such EU supply sites must hold appropriate approvals from the national competent authority(ies) under this Directive which should be verified as part of starting material supplier management.

    (b) Where such human cells or tissues are imported from third countries they must meet equivalent Community standards of quality and safety equivalent to those laid down in Directive 2004/23/EC. The traceability and serious adverse reaction and serious adverse event notification requirements are set out in Directive 2006/86/EC.

    (c) There may be some instances where processing of cells and tissues used as starting materials for biological medicinal products will be conducted at tissue establishments. Such processing steps, e.g. freezing, are under the scope of Directive 2004/23/EC, which provides for the need of a Responsible Person (RP).

    (d) Tissue and cells are released by the RP in the tissue establishment before shipment to the medicinal product manufacturer, after which normal medicinal product starting material controls apply. The test results of all tissues / cells supplied by the tissue establishment should be available to the manufacturer of the medicinal product. Such information must be used to make appropriate material segregation and storage decisions. In cases where manufacturing must be initiated prior to receiving test results from the tissue establishment, tissue and cells may be shipped to the medicinal product manufacturer provided controls are in place to prevent cross contamination with tissue and cells that have been released by the RP in the tissue establishment.

    (e) The transport of human tissues and cells to the manufacturing site must be controlled by a written agreement between the responsible parties. The manufacturing sites should have documentary evidence of adherence to the specified storage and transport conditions.

18 For blood-derived cells, compliance with Directive 2002/98 regarding donation, procurement and testing is likewise acceptable.

(f) Continuation of traceability requirements started at tissue establishments through to the recipient(s), and vice versa, including materials in contact with the cells or tissues, should be maintained.

(g) A technical agreement should be in place between the responsible parties (e.g., manufacturers, tissue establishment, Sponsors, MA Holder) which defines the tasks of each party, including the RP and Qualified Person.

37. Where human or animal cells are used in the manufacturing process as feeder cells, appropriate controls over the sourcing, testing, transport and storage should be in place, including control of compliance with donation, procurement and testing standards equivalent to ones set in the Directive 2004/23.

Seed lot and cell bank system

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

39. The number of generations (doublings, passages) between the seed lot or cell bank, the active biological substance and the finished product should be consistent with specifications in the MA or CTA.

40. As part of product lifecycle management, establishment of seed lots and cell banks, including master and working generations, should be performed under circumstances which are demonstrably appropriate. This should include an appropriately controlled environment to protect the seed lot and the cell bank and 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) should be handled simultaneously in the same area or by the same persons. For stages prior to the master seed or cell bank generation, where only the principles of GMP may be applied, documentation should be available to support traceability including issues related to components used during development with potential impact on product safety (e.g. reagents of biological origin) from initial sourcing and genetic development if applicable. For vaccines the requirements of Ph Eur monograph 2005;153 “Vaccines for human use” will apply.

41. Following the establishment of master and working cell banks and master and working seed lots, quarantine and release procedures should be followed. This should include adequate characterization and testing for contaminants. Their on-going suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product. Evidence of the stability and recovery of the seeds and banks should be documented and records should be kept in a manner permitting trend evaluation.

42. Seed lots and cell banks should be stored and used in such a way as to minimize the risks of contamination, (e.g. stored in the vapour phase of liquid nitrogen in sealed containers) or alteration. Control measures for the storage of different seeds and/or cells in the same area or equipment should prevent mix-up and take account the infectious nature of the materials to prevent cross contamination.

43. Storage containers should be sealed, clearly labelled and kept at an appropriate temperature. A stock inventory must be kept. The storage temperature should be recorded continuously and, where used, the liquid nitrogen level monitored. Deviation from set limits and corrective and preventive action taken should be recorded.
44. It is desirable to split stocks and to store the split stocks at different locations so as to minimize the risks of total loss. The controls at such locations should provide the assurances outlined in the preceding paragraphs.
45. The storage and handling conditions for stocks should be managed according to the same procedures and parameters. Once containers are removed from the seed lot / cell bank management system, the containers should not be returned to stock. Operating principles
46. Change management should, on a periodic basis, take into account the effects, including cumulative effects of changes (e.g. to the process) on the quality, safety and efficacy of the finished product.
47. Critical operational (process) parameters, or other input parameters which affect product quality, need to be identified, validated, documented and be shown to be maintained within requirements.
48. A control strategy for the entry of articles and materials into production areas should be based on QRM principles. For aseptic processes, heat stable articles and materials entering a clean area or clean/contained area should preferably do so through a double ended autoclave or oven. Heat labile articles and materials should enter through an air lock with interlocked doors where they are subject to effective surface sanitisation procedures. Sterilisation of articles and materials elsewhere is acceptable provided that they are multiple wrappings, as appropriate to the number of stages of entry to the clean area, and enter through an airlock with the appropriate surface sanitisation precautions.
49. The growth promoting properties of culture media should be demonstrated to be suitable for its intended use. If possible, media should be sterilized in situ. In-line sterilizing filters for routine addition of gases, media, acids or alkalis, anti-foaming agents etc. to fermenters should be used where possible.
50. Addition of materials or cultures to fermenters and other vessels and sampling should be carried out under carefully controlled conditions to prevent contamination. Care should be taken to ensure that vessels are correctly connected when addition or sampling takes place.
51. Continuous monitoring of some production processes (e.g. fermentation) may be necessary, such data should form part of the batch record. Where continuous culture is used, special consideration should be given to the quality control requirements arising from this type of production method.
52. Centrifugation and blending of products can lead to aerosol formation and containment of such activities to minimise cross-contamination is necessary.
53. Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Qualified decontamination measures should be available for each organism or groups of related organisms. Where different strains of single bacteria species or very similar viruses are involved, the decontamination process may be validated with one

representative strain, unless there is reason to believe that they may vary significantly in their resistance to the agent(s) involved.

54. If obviously contaminated, such as by spills or aerosols, or if a potential hazardous organism is involved, production and control materials, including paperwork, must be adequately disinfected, or the information transferred out by other means.

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

56. For products that are inactivated by the addition of a reagent (e.g. micro-organisms in the course of vaccine manufacture) the process should ensure the complete inactivation of live organism. In addition to the thorough mixing of culture and inactivant, consideration should be given to contact of all product-contact surfaces exposed to live culture and, where required, the transfer to a second vessel.

57. A wide variety of equipment is used for chromatography. QRM principles should be used to devise the control strategy on matrices, the housings and associated equipment when used in campaign manufacture and in multi-product environments. The re-use of the same matrix at different stages of processing is discouraged. Acceptance criteria, operating conditions, regeneration methods, life span and sanitization or sterilization methods of columns should be defined.

58. Where irradiated equipment and materials are used, Annex 12 to EudraLex, Volume 4, should be consulted for further guidance.

59. There should be a system to assure the integrity and closure of containers after filling where the final products or intermediates represent a special risk and procedures to deal with any leaks or spillages. Filling and packaging operations need to have procedures in place to maintain the product within any specified limits, e.g. time and/or temperature.

60. Activities in handling vials containing live biological agents must be performed in such a way to prevent the contamination of other products or egress of the live agents into the work environment or the external environment. The viability of such organisms and their biological classification should take into consideration as part of the management of such risks.

61. Care should be taken in the preparation, printing, storage and application of labels, including any specific text for patient-specific product of the contents on the immediate and outer packaging. In the case of autologous products, the unique patient identifier and the statement “for autologous use only” should be indicated on the outer packaging or, where there is no outer packaging, on the immediate packaging.

62. The compatibility of labels with ultra-low storage temperatures, where such temperatures are used, should be verified.

63. Where donor (human or animal) health information becomes available after procurement, which affects product quality, it should be taken into account in recall procedures. Quality control

64. In-process controls have a greater importance in ensuring the consistency of the quality of biological active substance and medicinal products than for conventional products. In-process control testing should be performed at appropriate stages of

production to control those conditions that are important for the quality of the finished product.

65. Where intermediates can be stored for extended periods of time (days, weeks or longer), consideration should be given to the inclusion of finished product batches made from materials held for their maximum in-process periods in the on-going stability programme.

66. Certain types of cells (e.g. autologous cells) may be available in limited quantities and, where allowed in the MA, a modified testing and sample retention strategy may be developed and documented.

67. For cellular products, sterility tests should be conducted on antibiotic-free cultures of cells or cell banks to provide evidence for absence of bacterial and fungal contamination and to be able to detection fastidious organisms where appropriate.

68. For biological medicinal products with a short shelf life, which for the purposes of the annex is taken to mean a period of 14 days or less, and which need batch certification before completion of all end product quality control tests (e.g. sterility tests) a suitable control strategy must be in place. Such controls need to be built on enhanced understanding of product and process performance and take into account the controls and attributes of starting and raw materials. The exact and detailed description of the entire release procedure, including the responsibilities of the different personnel involved in assessment of production and analytical data is essential. A continuous assessment of the effectiveness of the quality assurance system must be in place including records kept in a manner which permit trend evaluation.

    Where end product tests are not available due to their short shelf life, alternative methods of obtaining equivalent data to permit initial batch certification should be considered (e.g. rapid microbiological methods). The procedure for batch certification and release may be carried out in two or more stages -:

    a) Assessment by designated person(s) of batch processing records, results from environmental monitoring (where available) which should cover production conditions, all deviations from normal procedures and the available analytical results for review in preparation for the initial certification by the Qualified Person.

    b) Assessment of the final analytical tests and other information available for final certification by the Qualified Person. A procedure should be in place to describe the measures to be taken (including liaison with clinical staff) where out of specification test results are obtained. Such events should be fully investigated and the relevant corrective and preventive actions taken to prevent recurrence documented.

PART B. SPECIFIC GUIDANCE ON SELECTED PRODUCT TYPES

B1. ANIMAL SOURCED PRODUCTS[19]

This guidance applies to animal materials which includes materials from establishments such as abattoirs. Since the supply chains can be extensive and complex, controls based on QRM principles need to be applied, see also requirements of Ph Eur monographs, including the need for specific tests at defined stages. Documentation to demonstrate the supply chain traceability[20] and clear roles of participants in the supply chain, typically including a sufficiently detailed and current process map, should be in place.

1. Monitoring programmes should be in place for animal disease that are of concern to human health. Organisations should take into account reports from trustworthy sources on national disease prevalence when compiling their assessment of risk and mitigation factors. Such organisations include the World Organisation for Animal Health (OIE, Office International des Epizooties[21]). This should be supplemented by information on health monitoring and control programme(s) at national and local levels, the latter to include the sources (e.g. farm or feedlot) from which the animals are drawn and the control measures in place during transport to the abattoirs.
2. Where abattoirs are used to source animal tissues, they should be shown to operate to standards equivalent to those used in the EU. Account should be taken of reports from organisations such as the Food and Veterinary Office[22] who verify compliance with the requirements of food safety and quality, veterinary and plant health legislation within the EU and in third countries exporting to the EU.
3. Control measures for starting or raw materials at establishments such as abattoirs should include appropriate elements of a Quality Management System to assure a satisfactory level of operator training, materials traceability, control and consistency. These measures may be drawn from sources outside EU GMP but should be shown to provide equivalent levels of control.
4. Control measures for starting or raw materials should be in place which prevent interventions which may affect the quality of materials, or which at least provides evidence of such activities, during their progression through the manufacturing and supply chain. This includes the movement of material between sites of initial collection, partial and final purification(s), storage sites, hubs, consolidators and brokers. Details of such arrangements should be recorded within the traceability system and any breaches recorded, investigated and actions taken.
5. Regular audits of the starting or raw material supplier should be undertaken which verify compliance with controls for materials at the different stages of manufacture. Issues must be investigated to a depth appropriate to their significance, for which full documentation should be available. Systems should also be in place to ensure that effective corrective and preventive actions are taken.

19 See also PhEur monograph requirements, 0333
20 See Chapter 5 in EudraLex, Volume 4.
21 http://www.oie.int/eng/en_index.htm
22 http://ec.europa.eu/food/fvo/index_en.htm

B2. ALLERGEN PRODUCTS

Materials may be manufactured by extraction from natural sources or manufactured by recombinant DNA technology.

1. Source materials should be described in sufficient detail to ensure consistency in their supply, e.g. common and scientific name, origin, nature, contaminant limits, method of collection. Those derived from animals should be from healthy sources. Appropriate biosecurity controls should be in place for colonies (e.g. mites, animals) used for the extraction of allergens. Allergen products should be stored under defined conditions to minimise deterioration.
2. The production process steps including pre-treatment, extraction, filtration, dialysis, concentration or freeze-drying steps should be described in detail and validated.
3. The modification processes to manufacture modified allergen extracts (e.g. allergoids, conjugates) should be described. Intermediates in the manufacturing process should be identified and controlled.
4. Allergen extract mixtures should be prepared from individual extracts from single source materials. Each individual extract should be considered as one active substance.

B3. ANIMAL IMMUNOSERA PRODUCTS

1. Particular care should be exercised on the control of antigens of biological origin to assure their quality, consistency and freedom from adventitious agents. The preparation of materials used to immunise the source animals (e.g. antigens, hapten carriers, adjuvants, stabilising agents), the storage of such material immediately prior to immunisation should be in accordance with documented procedures.
2. The immunisation, test bleed and harvest bleed schedules should conform to those approved in the CTA or MA.
3. The manufacturing conditions for the preparation of antibody sub-fragments (e.g. Fab or F(ab')2) and any further modifications must be in accordance with validated and approved parameters. Where such enzymes are made up of several components, their consistency should be assured.

B4. VACCINES

1. Where eggs are used, the health status of all source flocks used in the production of eggs (whether specified pathogen free or healthy flocks) should be assured.
2. The integrity of containers used to store intermediate products and the hold times must be validated.
3. Vessels containing inactivated products should not be opened or sampled in areas containing live biological agents.
4. The sequence of addition of active ingredients, adjuvants and excipients during the formulation of an intermediate or final product must be in compliance with specifications.
5. Where organisms with a higher biological safety level (e.g. pandemic vaccine strains) are to be used in manufacture or testing, appropriate containment arrangements must be in place. The approval of such arrangements should be obtained from the appropriate national authority(ies) and the approval documents be available for verification.

B5. RECOMBINANT PRODUCTS

1. Process condition during cell growth, protein expression and purification must be maintained within validated parameters to assure a consistent product with a defined range of impurities that is within the capability of the process to reduce to acceptable levels. The type of cell used in production may require increased measures to be taken to assure freedom from viruses. For production involving multiple harvest, the period of continuous cultivation should be within specified limits.
2. The purification processes to remove unwanted host cell proteins, nucleic acids, carbohydrates, viruses and other impurities should be within defined validated limits.

B6. MONOCLONAL ANTIBODY PRODUCTS

1. Monoclonal antibodies may be manufactured from murine hybridomas, human hybridomas or by recombinant DNA technology. Control measures appropriate to the different source cells (including feeder cells if used) and materials used to establish the hybridoma / cell line should be in place to assure the safety and quality of the product. It should be verified that these are within approved limits. Freedom from viruses should be given particular emphasis. It should be noted that data originating from products generated by the same manufacturing technology platform may be acceptable to demonstrate suitability.
2. Criteria to be monitored at the end of a production cycle and for early termination of production cycles should be verified that these are within approved limits.
3. The manufacturing conditions for the preparation of antibody sub-fragment (e.g. Fab, F(ab')2, scFv) and any further modifications (e.g. radio labelling, conjugation, chemical linking) must be in accordance with validated parameters.

B7. TRANSGENIC ANIMAL PRODUCTS

Consistency of starting material from a transgenic source is likely to be more problematic than is normally the case for non-transgenic biotechnology sources. Consequently, there is an increased requirement to demonstrate batch-to-batch consistency of product in all respects.

1. A range of species may be used to produce biological medicinal products, which may be expressed into body fluids (e.g. milk) for collection and purification. Animals should be clearly and uniquely identified and backup arrangements should be put in place in the event of loss of the primary marker.
2. The arrangements for housing and care of the animals should be defined such that they minimise the exposure of the animals to pathogenic and zoonotic agents. Appropriate measures to protect the external environment should be established. A health monitoring programme should be established and all results documented, any incident should be investigated and its impact on the continuation of the animal and on previous batches of product should be determined. Care should be taken to ensure that any therapeutic products used to treat the animals do not contaminate the product.
3. The genealogy of the founder animals through to production animals must be documented. Since a transgenic line will be derived from a single genetic founder animal, materials from different transgenic lines should not be mixed.

4. The conditions under which the product is harvested should be in accordance with MA or CTA conditions. The harvest schedule and conditions under which animals may be removed from production should be performed according to approved procedures and acceptance limits.

B8. TRANSGENIC PLANT PRODUCTS

Consistency of starting material from a transgenic source is likely to be more problematic than is normally the case for non-transgenic biotechnology sources. Consequently, there is an increased requirement to demonstrate batch-to-batch consistency of product in all respects.

1. Additional measures, over and above those given in Part A, may be required to prevent contamination of master and working transgenic banks by extraneous plant materials and relevant adventitious agents. The stability of the gene within defined generation numbers should be monitored.
2. Plants should be clearly and uniquely identified, the presence of key plant features, including health status, across the crop should be verified at defined intervals through the cultivation period to assure consistency of yield between crops.
3. Security arrangements for the protection of crops should be defined, wherever possible, such that they minimise the exposure to contamination by microbiological agents and cross-contamination with non-related plants. Measures should be in place to prevent materials such as pesticides and fertilisers from contaminating the product. A monitoring programme should be established and all results documented, any incident should be investigated and its impact on the continuation of the crop in the production programme should be determined.
4. Conditions under which plants may be removed from production should be defined. Acceptance limits should be set for materials (e.g. host proteins) that may interfere with the purification process. It should be verified that the results are within approved limits.
5. Environmental conditions (temperature, rain), which may affect the quality attributes and yield of the recombinant protein from time of planting, through cultivation to harvest and interim storage of harvested materials should be documented. The principles in documents such as 'Guideline on Good Agricultural and Collection Practice for Starting Materials of Herbal origin'**23** of the Committee of Herbal Medicinal Products should be taken into account when drawing up such criteria.

23 Doc. Ref. EMEA/HMPC/246816/2005.

GLOSSARY TO ANNEX 2.

Entries are only included where the terms are used in Annex 2 and require further explanation. Definitions which already exist in legislation or other sources are cross referenced. In addition to this glossary, the GMP-glossary in EudraLex, Volume 4[24] applies, unless indicated otherwise.

Active substance. See Article 1(3a) of Directive 2001/83/EC.

Adjuvant. A chemical or biological substance that enhances the immune response against an antigen.

Allergoids. Allergens which are chemically modified to reduce IgE reactivity. Antigens. Substances (e.g. toxins, foreign proteins, bacteria, tissue cells) capable of inducing specific immune responses.

Antibody. Proteins produced by the B-lymphocytes that bind to specific antigens. Antibodies may divided into 2 main types based on key differences in their method of manufacture:

Monoclonal antibodies (MAb) – homogenous antibody population obtained from a single clone of lymphocytes or by recombinant technology and which bind to a single epitope.

Polyclonal antibodies – derived from a range of lymphocyte clones, produced in human and animals in response to the epitopes on most 'non-self' molecules.

Area. A specific set of rooms within a building associated with the manufacturing of any one product or multiple products that has a common air handling unit.

Bioburden. The level and type (i.e. objectionable or not) of micro-organism present in raw materials, media, biological substances, intermediates or products. Regarded as contamination when the level and/or type exceed specifications.

Biological medicinal product. See 3rd paragraph of point 3.2.1.1.b. of Part I of Annex I to Directive 2001/83/EC.

Biosafety level (BSL). The containment conditions required to safely handle organisms of different hazards ranging from BSL1 (lowest risk, unlikely to cause human disease) to BSL4 (highest risk, cause severe disease, likely to spread and no effective prophylaxis or treatment available).

Campaigned manufacture. The manufacture of a series of batches of the same product in sequence in a given period of time followed by strict adherence to accepted control measures before transfer to another product. The products are not run at the same time but may be run on the same equipment.

Cell bank - a collection of appropriate containers, whose contents are of uniform composition, stored under defined conditions. Each container represents an aliquot of a single pool of cells.

Cell stock - primary cells expanded to a given number of cells to be aliquoted and used as starting material for production of a limited number of lots of a cell based medicinal product.

Closed system. Where a drug substance or product is not exposed to the immediate room environment during manufacture.

Contained use: See Article 2(c) of Directive 2009/41/EC for all genetically modified organisms.

Deliberate release. See Article 2(3) of Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.[24]

24 http://ec.europa.eu/heal th/files/eudralex/vol-4/pdfs-en/glos4en200408_en.pdf.

Excipient. See Article 1(3b) of Directive 2001/83/EC.

Ex-vivo. Where procedures are conducted on tissues or cells outside the living body and returned to the living body.

Feeder cells. Cells used in co-culture to maintain pluripotent stem cells. For human embryonic stem cell culture, typical feeder layers include mouse embryonic fibroblasts (MEFs) or human embryonic fibroblasts that have been treated to prevent them from dividing.

Gene. A sequence of DNA that codes for one (or more) protein(s).

Genetically modified organism (GMO). See Article 2(2) of Directive 2001/18/EC.

Hapten. A low molecular weight molecule that is not in itself antigenic unless conjugated to a 'carrier' molecule.

Hybridoma. An immortalised cell line that secrete desired (monoclonal) antibodies and are typically derived by fusing B-lymphocytes with tumour cells.

Intermediate product - see definitions in GMP Glossary and in Part II.

In-vivo. Procedures conducted in living organisms.

Look-back: documented procedure to trace biological medicinal substances or products which may be adversely affected by the use or incorporation of animal or human materials when either such materials fail release tests due to the presence of contaminating agent(s) or when conditions of concern become apparent in the source animal or human.

Master cell bank (MCB) –An aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions. The MCB is used to derive all working cell banks.

Master virus seed (MVS) – as above, but in relation to viruses;

master transgenic bank – as above but for transgenic plants or animals.

Monosepsis (axenic). A single organism in culture which is not contaminated with any other

Multi-product facility. A facility that manufactures, either concurrently or in campaign mode, a range of different biological medicinal substances and products and within which equipment train(s) may or may not be dedicated to specific substances or products.

Plasmid. A plasmid is a piece of DNA usually present in a bacterial cell as a circular entity separated from the cell chromosome; it can be modified by molecular biology techniques, purified out of the bacterial cell and used to transfer its DNA to another cell.

Raw materials. See 4th paragraph of point 3.2.1.1.b. of Part I of Annex I to Directive 2001/83/EC.

Responsible Person (RP). The person designated in accordance with Article 17 of Directive 2004/23/EC.

Scaffold – a support, delivery vehicle or matrix that may provide structure for or facilitate the migration, binding or transport of cells and/or bioactive molecules.

Somatic cells. Cells, other than reproductive (germ line) cells, which make up the body of a human or animal. These cells may be autologous (from the patient), allogeneic (from another human being) or xenogeneic (from animals) somatic living cells, that have been manipulated or altered ex vivo, to be administered in humans to obtain a therapeutic, diagnostic or preventive effects.

Specified pathogen free (SPF)- Animal materials (e.g. chickens, embryos or cell cultures) used for the production or quality control of biological medicinal products derived from

groups (e.g. flocks or herds) of animals free from specified pathogens. Such flocks or herds are defined as animals sharing a common environment and having their own caretakers who have no contact with non-SPF groups.

Starting materials. See the 1st and 2nd paragraph of point 3.2.1.1.b of Part I of Annex I to Directive 2001/83/EC.

Transgenic: an organism that contains a foreign gene in its normal genetic component for the expression of biological pharmaceutical materials.

Working cell bank (WCB) – a homogeneous pool of micro-organisms or cells, that are distributed uniformly into a number of containers derived from a MCB that are stored in such a way to ensure stability and for use in production. **Working virus seed (WVS) –** as above but in relation to viruses, **working transgenic bank –** as above but for transgenic plants or animals.

Zoonosis: Animal diseases that can be transmitted to humans

Annex 3
Manufacture of Radiopharmaceuticals

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 should 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 should 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: *ƒ* Radiopharmaceuticals *ƒ* Positron Emitting (PET) Radiopharmaceuticals *ƒ* Radioactive Precursors for radiopharmaceutical production *ƒ* Radionuclide Generators

Type of manufacture	Non - GMP*	GMP part II & I (Increasing) including relevant annexes			
Radiopharmaceuticals PET Radiopharmaceuticals Radioactive Precursors	Reactor/ Cyclotron Production	Chemical synthesis	Purification steps	Processing, formulation and dispensing	Aseptic or final sterilization
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 should 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 should comply with sterility requirements for parenterals and, where relevant, aseptic working conditions for the manufacture of sterile medicinal products, which are covered in Eudralex Volume 4, 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 should in addition be produced in accordance with the principles in Eudralex Volume 4, 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 should be applied to the manufacturing of radiopharmaceuticals and a risk management approach should be used to determine the extent of qualification/validation, focusing on a combination of Good Manufacturing Practice and Radiation Protection.

Personnel

13. All manufacturing operations should be carried out under the responsibility of personnel with additional competence in radiation protection. Personnel involved in production, analytical control and release of radiopharmaceuticals should be appropriately trained in radiopharmaceutical specific aspects of the quality management system. The QP should 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 should receive appropriate additional training specific to these types of procedures and 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 should be manufactured in controlled (environmental and radioactive) areas. All manufacturing steps should take place in self-contained facilities dedicated to radiopharmaceuticals
17. Measures should be established and implemented to prevent cross-contamination from personnel, materials, radionuclides etc. Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, precautions should be taken to minimize the risk of contamination. The risk assessment should demonstrate that the environmental cleanliness level proposed is suitable for the type of product being manufactured.
18. Access to the manufacturing areas should be via a gowning area and should be restricted to authorised personnel.
19. Workstations and their environment should be monitored with respect to radioactivity, particulate and microbiological quality as established during performance qualification (PQ).
20. Preventive maintenance, calibration and qualification programmes should be operated to ensure that all facilities and equipment used in the manufacture of radiopharmaceutical are suitable and qualified. These activities should be carried out by competent personnel and records and logs should be maintained.
21. Precautions should be taken to avoid radioactive contamination within the facility. Appropriate controls should be in place to detect any radioactive contamination, either directly through the use of radiation detectors or indirectly through a swabbing routine.
22. Equipment should 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 should be avoided unless justified. Air outlets should be designed to minimize

environmental contamination by radioactive particles and gases and appropriate measures should 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 should 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 should comply with the requirements described in the Eudralex Volume 4, Annex 1.
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 closed and automated systems (chemical synthesis, purification, on-line sterile filtration) a grade C environment (usually “Hot-cell”) will be suitable. Hot-cells should 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 should be prepared, reviewed, approved and distributed according to written procedures.
30. Specifications should be established and documented for raw materials, labelling and packaging materials, critical intermediates and the finished radiopharmaceutical. Specifications should also be in place for any other critical items used in the manufacturing process, such as process aids, gaskets, sterile filtering kits, that could critically impact on quality.
31. Acceptance criteria should 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 should 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 should 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 should be avoided in order to minimise the risk of radioactive cross-contamination or mix-up.
35. Special attention should be paid to validation including validation of computerised systems which should be carried out in accordance in compliance with Eudralex Volume 4, annex 11. New manufacturing processes should be validated prospectively.
36. The critical parameters should normally be identified before or during validation and the ranges necessary for reproducible operation should be defined.
37. Integrity testing of the membrane filter should 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 labelled 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 should 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. Where certain test results are not available before use of the product, the Qualified Person should conditionally certify the product before it is used and should 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 should 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 should be performed as soon as possible.
43. A written procedure detailing the assessment of production and analytical data, which should be considered before the batch is dispatched, should be established.
44. Products that fail to meet acceptance criteria should be rejected. If the material is reprocessed, preestablished procedures should be followed and the finished product should meet acceptance criteria before release. Returned products may not be reprocessed and must be stored as radioactive waste.

45. A procedure should 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 should be investigated to include the relevant corrective and preventative actions taken to prevent future events. This process must be documented.
46. Information should be given to the clinical responsible persons, if necessary. To facilitate this, a traceability system should be implemented for radiopharmaceuticals.
47. A system to verify the quality of starting materials should be in place. Supplier approval should include an evaluation that provides adequate assurance that the material consistently meets specifications. The starting materials, packaging materials and critical process aids should 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

Preparation: handling and radio labelling of kits with radionuclide eluted from generators or radioactive precursors within a hospital. Kits, generators and precursors should have a marketing authorisation or a national licence.
Manufacturing: production, quality control and release and delivery of radiopharmaceuticals from the active substance and starting materials.
Hot –cells: shielded workstations for manufacture and handling of radioactive materials. Hot-cells are not necessarily designed as an isolator.
Qualified person: QP as described in Directives 2001/83/EC and 2001/82/EC. QP responsibilities are elaborated in Eudralex Volume 4, annex 16.

ANNEX 4
MANUFACTURE OF VETERINARY MEDICINAL PRODUCTS OTHER THAN IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Note

This annex applies to all veterinary medicinal products falling within the scope of Directive 2001/82/EC other than immunological veterinary medicinal products, which are the subject of a separate annex.

Manufacture of premixes for medicated feeding stuffs

For the purposes of these paragraphs,

— a medicated feeding stuff is any mixture of a veterinary medicinal product or products and feed or feeds which is ready prepared for marketing and intended to be fed to animals without further processing because of its curative or preventative properties or other properties as a medicinal product covered by Article 1 (2) of Directive 2001/82/EC;

— a pre-mix for medicated feeding stuffs is any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feeding stuffs.

1. The manufacture of premixes for medicated feeding stuffs requires the use of large quantities of vegetable matter which is likely to attract insects and rodents. Premises should be designed, equipped and operated to minimise this risk (point 3.4.) and should also be subject to a regular pest control programme.
2. Because of the large volume of dust generated during the production of bulk material for premixes, specific attention should be given to the need to avoid cross contamination and facilitate cleaning (point 3.14), for example through the installation of sealed transport systems and dust extraction, whenever possible. The installation of such systems does not, however, eliminate the need for regular cleaning of production areas.
3. Parts of the process likely to have a significant adverse influence on the stability of the active ingredient(s) (e.g. use of steam in pellet manufacture) should be carried out in an uniform manner from batch to batch.
4. Consideration should be given to undertake the manufacture of premixes in dedicated areas which, if at all possible, do not form part of a main manufacturing plant. Alternatively, such dedicated areas should be surrounded by a buffer zone in order to minimise the risk of contamination of other manufacturing areas.

Manufacture of ectoparasiticides

5. In derogation from point 3.6, ectoparasiticides for external application to animals, which are veterinary medicinal products, and subject to marketing authorisation, may be produced and filled on a campaign basis in pesticide specific areas. However other categories of veterinary medicinal products should not be produced in such areas.
6. Adequate validated cleaning procedures should be employed to prevent cross contamination, and steps should be taken to ensure the secure storage of the veterinary medicinal product in accordance with the guide.

Manufacture of veterinary medicinal products containing penicillins

7. The use of penicillins in veterinary medicine does not present the same risks of hypersensitivity in animals as in humans. Although incidents of hypersensitivity have been recorded in horses and dogs, there are other materials which are toxic to certain species, e.g. the ionophore antibiotics in horses. Although desirable, the requirements that such products be manufactured in dedicated, self-contained facilities (point 3.6) may be dispensed with in the case of facilities dedicated to the manufacture of veterinary medicinal products only. However, all necessary measures should be taken to avoid cross contamination and any risk to operator safety in accordance with the guide. In such circumstances, penicillin-containing products should be manufactured on a campaign basis and should be followed by appropriate, validated decontamination and cleaning procedures.

Retention of samples (point 1.4 viii and point 6.14)

8. It is recognised that because of the large volume of certain veterinary medicinal products in their final packaging, in particular premixes, it may not be feasible for manufacturers to retain samples from each batch in its final packaging. However, manufacturers should ensure that sufficient representative samples of each batch are retained and stored in accordance with the guide.
9. In all cases, the container used for storage should be composed of the same material as the market primary container in which the product is marketed.

Sterile veterinary medicinal products

10. Where this has been accepted by the competent authorities, terminally sterilised veterinary medicinal products may be manufactured in a clean area of a lower grade than the grade required in the annex on “Sterile preparations”, but at least in a grade D environment.

ANNEX 5
MANUFACTURE OF IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Principle

The manufacture of immunological veterinary medicinal products has special characteristics which should be taken into consideration when implementing and assessing the quality assurance system.

Due to the large number of animal species and related pathogenic agents, the variety of products manufactured is very wide and the volume of manufacture is often low; hence, work on a campaign basis is common. Moreover, because of the very nature of this manufacture (cultivation steps, lack of terminal sterilisation, etc.), the products must be particularly well-protected against contamination and cross-contamination. The environment also must be protected especially when the manufacture involves the use of pathogenic or exotic biological agents and the worker must be particularly well protected when the manufacture involves the use of biological agents pathogenic to man.

These factors, together with the inherent variability of immunological products and the relative inefficiency in particular of final product quality control tests in providing adequate information about products, means that the role of the quality assurance system is of the utmost importance. The need to maintain control over all of the following aspects of GMP, as well as those outlined in this Guide, cannot be overemphasised. In particular, it is important that the data generated by the monitoring of the various aspects of GMP (equipment, premises, product etc.) are rigorously assessed and informed decisions, leading to appropriate action, are made and recorded.

Personnel

1. All personnel (including those concerned with cleaning and maintenance) employed in areas where immunological products are manufactured should be given training in and information on hygiene and microbiology. They should receive additional training specific to the products with which they work.
2. Responsible personnel should be formally trained in some or all of the following fields: bacteriology, biology, biometry, chemistry, immunology, medicine, parasitology, pharmacy, pharmacology, virology and veterinary medicine and should also have an adequate knowledge of environmental protection measures.
3. Personnel should be protected against possible infection with the biological agents used in manufacture. In the case of biological agents known to cause disease in humans, adequate measures should be taken to prevent infection of personnel working with the agent or with experimental animals.

   Where relevant, the personnel should be vaccinated and subject to medical examination.
4. Adequate measures should be taken to prevent biological agents being taken outside the manufacturing plant by personnel acting as a carrier. Dependent on the type of biological agent, such measures may include complete change of clothes and compulsory showering before leaving the production area.

5. For immunological products, the risk of contamination or cross-contamination by personnel is particularly important.

   Prevention of contamination by personnel should be achieved by a set of measures and procedures to ensure that appropriate protective clothing is used during the different stages of the production process.

   Prevention of cross-contamination by personnel involved in production should be achieved by a set of measures and procedures to ensure that they do not pass from one area to another unless they have taken appropriate measures to eliminate the risk of contamination. In the course of a working day, personnel should not pass from areas where contamination with live micro-organisms is likely or where animals are housed to premises where other products or organisms are handled. If such passage is unavoidable, clearly defined decontamination procedures, including change of clothing and shoes, and, where necessary, showering, should be followed by staff involved in any such production.

   Personnel entering a contained area where organisms had not been handled in open circuit operations in the previous twelve hours to check on cultures in sealed, surface decontaminated flasks would not be regarded as being at risk of contamination, unless the organism involved was an exotic.

Premises

6. Premises should be designed in such a way as to control both the risk to the product and to the environment. This can be achieved by the use of containment, clean, clean/contained or controlled areas.
7. Live biological agents should be handled in contained areas. The level of containment should depend on the pathogenicity of the micro-organism and whether it has been classified as exotic. (Other relevant legislation, such as Directives 90/219/EEC[1] and 90/220/EEC[2], also applies).
8. Inactivated biological agents should be handled in clean areas. Clean areas should also be used when handling non-infected cells isolated from multicellular organisms and, in some cases, filtration-sterilised media.
9. Open circuit operations involving products or components not subsequently sterilised should be carried out within a laminar air flow work station (grade A) in a grade B area.

[1] Council Directive 98/81/EC of 26 October 1998 amending Directive 90/219/EEC on the contained use of genetically modified micro-organisms (OJ L 330, 05.12.1998, p. 13-31)

[2] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC – Commission Declaration (OJ L 106, 17.04.2001, p. 01-39)

10. Other operations where live biological agents are handled (quality control, research and diagnostic services, etc.) should be appropriately contained and separated if production operations are carried out in the same building. The level of containment should depend on the pathogenicity of the biological agent and whether they have been classified as exotic. Whenever diagnostic activities are carried out, there is the risk of introducing highly pathogenic organisms. Therefore, the level of containment should be adequate to cope with all such risks. Containment may also be required if quality control or other activities are carried out in buildings in close proximity to those used for production.

11. Containment premises should be easily disinfected and should have the following characteristics:
    a) the absence of direct venting to the outside;
    b) a ventilation with air at negative pressure. Air should be extracted through HEPA filters and not be re circulated except to the same area, and provided further HEPA filtration is used (normally this condition would be met by routing the re circulated air through the normal supply HEPAs for that area). However, recycling of air between areas may be permissible provided that it passes through two exhaust HEPAs, the first of which is continuously monitored for integrity, and there are adequate measures for safe venting of exhaust air should this filter fail;
    c) air from manufacturing areas used for the handling of exotic organisms should be vented through 2 sets of HEPA filters in series, and that from production areas not re-circulated;
    d) a system for the collection and disinfection of liquid effluents including contaminated condensate from sterilizers, biogenerators, etc. Solid wastes, including animal carcasses, should be disinfected, sterilized or incinerated as appropriate. Contaminated filters should be removed using a safe method;
    e) changing rooms designed and used as air locks, and equipped with washing and showering facilities if appropriate. Air pressure differentials should be such that there is no flow of air between the work area and the external environment or risk of contamination of outer clothing worn outside the area;
    f) an air lock system for the passage of equipment, which is constructed so that there is no flow of contaminated air between the work area and the external environment or risk of contamination of equipment within the lock. The air lock should be of a size which enables the effective surface decontamination of materials being passed through it. Consideration should be given to having a timing device on the door interlock to allow sufficient time for the decontamination process to be effective.
    g) in many instances, a barrier double-door autoclave for the secure removal of waste materials and introduction of sterile items.

12. Equipment passes and changing rooms should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time. Changing rooms should be supplied with air filtered to the same standard as that for the work area, and equipped with air extraction facilities to produce an adequate air circulation

independent of that of the work area. Equipment passes should normally be ventilated in the same way, but unventilated passes, or those equipped with supply air only, may be acceptable.

13. Production operations such as cell maintenance, media preparation, virus culture, etc. likely to cause contamination should be performed in separate areas. Animals and animal products should be handled with appropriate precautions.
14. Production areas where biological agents particularly resistant to disinfection (e.g. sporeforming bacteria) are handled should be separated and dedicated to that particular purpose until the biological agents have been inactivated.
15. With the exception of blending and subsequent filling operations, one biological agent only should be handled at a time within an area.
16. Production areas should be designed to permit disinfection between campaigns, using validated methods.
17. Production of biological agents may take place in controlled areas provided it is carried out in totally enclosed and heat sterilised equipment, all connections being also heat sterilised after making and before breaking. It may be acceptable for connections to be made under local laminar air flow provided these are few in number and proper aseptic techniques are used and there is no risk of leakage. The sterilisation parameters used before breaking the connections must be validated for the organisms being used. Different products may be placed in different biogenerators, within the same area, provided that there is no risk of accidental cross contamination. However, organisms generally subject to special requirements for containment should be in areas dedicated to such products.
18. Animal houses where animals intended or used for production are accommodated, should be provided with the appropriate containment and/or clean area measures, and should be separate from other animal accommodation

    Animal houses where animals used for quality control, involving the use of pathogenic biological agents, are accommodated, should be adequately contained.
19. Access to manufacturing areas should be restricted to authorised personnel. Clear and concise written procedures should be posted as appropriate.
20. Documentation relating to the premises should be readily available in a plant master file.

    The manufacturing site and buildings should be described in sufficient detail (by means of plans and written explanations) so that the designation and conditions of use of all the rooms are correctly identified as well as the biological agents which are handled in them. The flow of people and product should also be clearly marked.

    The animal species accommodated in the animal houses or otherwise on the site should be identified.

    The activities carried out in the vicinity of the site should also be indicated.

    Plans of contained and/or clean area premises, should describe the ventilation system indicating inlets and outlets, filters and their specifications, the number of air changes per hour, and pressure gradients. They should indicate which pressure gradients are monitored by pressure indicator.

Equipment

21. The equipment used should be designed and constructed so that it meets the particular requirements for the manufacture of each product.

    Before being put into operation the equipment should be qualified and validated and subsequently be regularly maintained and validated.

22. Where appropriate, the equipment should ensure satisfactory primary containment of the biological agents.

    Where appropriate, the equipment should be designed and constructed as to allow easy and effective decontamination and/or sterilisation.

23. Closed equipment used for the primary containment of the biological agents should be designed and constructed as to prevent any leakage or the formation of droplets and aerosols.

    Inlets and outlets for gases should be protected so as to achieve adequate containment e.g. by the use of sterilising hydrophobic filters.

    The introduction or removal of material should take place using a sterilisable closed system, or possibly in an appropriate laminar air flow.

24. Equipment where necessary should be properly sterilised before use, preferably by pressurised dry steam. Other methods can be accepted if steam sterilisation cannot be used because of the nature of the equipment. It is important not to overlook such individual items as bench centrifuges and water baths.

    Equipment used for purification, separation or concentration should be sterilised or disinfected at least between use for different products. The effect of the sterilisation methods on the effectiveness and validity of the equipment should be studied in order to determine the life span of the equipment.

    All sterilisation procedures should be validated.

25. Equipment should be designed so as to prevent any mix-up between different organisms or products. Pipes, valves and filters should be identified as to their function.

    Separate incubators should be used for infected and non infected containers and also generally for different organisms or cells. Incubators containing more than one organism or cell type will only be acceptable if adequate steps are taken to seal, surface decontaminate and segregate the containers. Culture vessels, etc. should be individually labelled. The cleaning and disinfection of the items can be particularly difficult and should receive special attention.

    Equipment used for the storage of biological agents or products should be designed and used in such a manner as to prevent any possible mix-up. All stored items should be clearly and unambiguously labelled and in leak-proof containers. Items such as cells and organisms seed stock should be stored in dedicated equipment.

26. Relevant equipment, such as that requiring temperature control, should be fitted with recording and/or alarm systems.

    To avoid breakdowns, a system of preventive maintenance, together with trend analysis of recorded data, should be implemented.

27. The loading of freeze dryers requires an appropriate clean/contained area.

    Unloading freeze dryers contaminates the immediate environment. Therefore, for single-ended freeze dryers, the clean room should be decontaminated before a further

manufacturing batch is introduced into the area, unless this contains the same organisms, and double door freeze dryers should be sterilised after each cycle unless opened in a clean area.

Sterilisation of freeze dryers should be done in accordance with item 24. In case of campaign working, they should at least be sterilised after each campaign.

Animals and animal houses

28. General requirements for animal quarters, care and quarantine are laid down in Directive 86/609/EEC[3].
29. Animal houses should be separated from the other production premises and suitably designed.
30. The sanitary status of the animals used for production should be defined, monitored, and recorded. Some animals should be handled as defined in specific monographs (e.g. Specific Pathogens Free flocks).
31. Animals, biological agents, and tests carried out should be the subject of an identification system so as to prevent any risk of confusion and to control all possible hazards. Disinfection – Waste disposal
32. Disinfection and/or wastes and effluents disposal may be particularly important in the case of manufacture of immunological products. Careful consideration should therefore be given to procedures and equipment aiming at avoiding environmental contamination as well as to their validation or qualification. Production
33. Because of the wide variety of products, the frequently large number of stages involved in the manufacture of immunological veterinary medicinal products and the nature of the biological processes, careful attention must be paid to adherence to validated operating procedures, to the constant monitoring of production at all stages and to in-process controls.

    Additionally, special consideration should be given to starting materials, media and the use of a seed lot system. Starting materials
34. The suitability of starting materials should be clearly defined in written specifications. These should include details of the supplier, the method of manufacture, the geographical origin and the animal species from which the materials are derived. The controls to be applied to starting materials must be included. Microbiological controls are particularly important.
35. The results of tests on starting materials must comply with the specifications. Where the tests take a long time (e.g. eggs from SPF flocks) it may be necessary to process starting materials before the results of analytical controls are available. In such cases, the release of a finished product is conditional upon satisfactory results of the tests on starting materials.

[3] Directive 2003/65/EC of the European Parliament and of the Council of 22 July 2003 amending Council Directive 86/609/EEC on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (OJ L 230 , 16.09.2003, p. 32-33)

36. Special attention should be paid to a knowledge of the supplier's quality assurance system in assessing the suitability of a source and the extent of quality control testing required.
37. Where possible, heat is the preferred method for sterilising starting materials. If necessary, other validated methods, such as irradiation, may be used.

Media

38. The ability of media to support the desired growth should be properly validated in advance.
39. Media should preferably be sterilised in situ or in line. Heat is the preferred method. Gases, media, acids, alkalis, defoaming agents and other materials introduced into sterile biogenerators should themselves be sterile.

Seed lot and cell bank system

40. In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of immunological veterinary medicinal products obtained by microbial, cell or tissue culture, or propagation in embryos and animals, should be based on a system of seed lots or cell banks.
41. The number of generations (doublings, passages) between the seed lot or cell bank and the finished product should be consistent with the dossier of authorisation for marketing.
42. Seed lots and cell banks should be adequately characterised and tested for contaminants. Acceptance criteria for new seed lots should be established. Seed lots and cell banks shall be established, stored and used in such a way as to minimise the risks of contamination, or any alteration. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus or cell lines) shall be handled simultaneously in the same area or by the same person.
43. Establishment of the seed lot and cell bank should be performed in a suitable environment to protect the seed lot and the cell bank and, if applicable, the personnel handling it and the external environment.
44. The origin, form and storage conditions of seed material should be described in full. Evidence of the stability and recovery of the seeds and cells should be provided. Storage containers should be hermetically sealed, clearly labelled and stored at an appropriate temperature. Storage conditions shall be properly monitored. An inventory should be kept and each container accounted for.
45. Only authorised personnel should be allowed to handle the material and this handling should be done under the supervision of a responsible person. Different seed lots or cell banks shall be stored in such a way to avoid confusion or cross-contamination errors. It is desirable to split the seed lots and cell banks and to store the parts at different locations so as to minimise the risk of total loss.

Operating principles

46. The formation of droplets and the production of foam should be avoided or minimised during manufacturing processes. Centrifugation and blending procedures which can

lead to droplet formation should be carried out in appropriate contained or clean/contained areas to prevent transfer of live organisms.

47. Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Validated decontamination measures should be available for each organism. Where different strains of single bacteria species or very similar viruses are involved, the process need be validated against only one of them, unless there is reason to believe that they may vary significantly in their resistance to the agent(s) involved.

48. Operations involving the transfer of materials such as sterile media, cultures or product should be carried out in pre-sterilised closed systems wherever possible. Where this is not possible, transfer operations must be protected by laminar airflow work stations.

49. Addition of media or cultures to biogenerators and other vessels should be carried out under carefully controlled conditions to ensure that contamination is not introduced. Care must be taken to ensure that vessels are correctly connected when addition of cultures takes place.

50. Where necessary, for instance when two or more fermenters are within a single area, sampling and addition ports, and connectors (after connection, before the flow of product, and again before disconnection) should be sterilised with steam. In other circumstances, chemical disinfection of ports and laminar air flow protection of connections may be acceptable.

51. Equipment, glassware, the external surfaces of product containers and other such materials must be disinfected before transfer from a contained area using a validated method (see 47 above). Batch documentation can be a particular problem. Only the absolute minimum required to allow operations to GMP standards should enter and leave the area. If obviously contaminated, such as by spills or aerosols, or if the organism involved is an exotic, the paperwork must be adequately disinfected through an equipment pass, or the information transferred out by such means as photocopy or fax.

52. Liquid or solid wastes such as the debris after harvesting eggs, disposable culture bottles, unwanted cultures or biological agents, are best sterilised or disinfected before transfer from a contained area. However, alternatives such as sealed containers or piping may be appropriate in some cases.

53. Articles and materials, including documentation, entering a production room should be carefully controlled to ensure that only articles and materials concerned with production are introduced. There should be a system which ensures that articles and materials entering a room are reconciled with those leaving so that their accumulation within the room does not occur.

54. Heat stable articles and materials entering a clean area or clean/contained area should do so through a double-ended autoclave or oven. Heat labile articles and materials should enter through an air-lock with interlocked doors where they are disinfected. Sterilisation of articles and materials elsewhere is acceptable provided that they are double wrapped and enter through an airlock with the appropriate precautions.

55. Precautions must be taken to avoid contamination or confusion during incubation. There should be a cleaning and disinfection procedure for incubators. Containers in incubators should be carefully and clearly labelled.

56. With the exception of blending and subsequent filling operations (or when totally enclosed systems are used) only one live biological agent may be handled within a production room at any given time. Production rooms must be effectively disinfected between the handling of different live biological agents.
57. Products should be inactivated by the addition of inactivant accompanied by sufficient agitation. The mixture should then be transferred to a second sterile vessel, unless the container is of such a size and shape as to be easily inverted and shaken so as to wet all internal surfaces with the final culture/inactivant mixture.
58. Vessels containing inactivated products should not be opened or sampled in areas containing live biological agents. All subsequent processing of inactivated products should take place in clean areas grade A-B or enclosed equipment dedicated to inactivated products.
59. Careful consideration should be given to the validation of methods for sterilisation, disinfection, virus removal and inactivation.
60. Filling should be carried out as soon as possible following production. Containers of bulk product prior to filling should be sealed, appropriately labelled and stored under specified conditions of temperature.
61. There should be a system to assure the integrity and closure of containers after filling.
62. The capping of vials containing live biological agents must be performed in such a way that ensures that contamination of other products or escape of the live agents into other areas or the external environment does not occur.
63. For various reasons there may be a delay between the filling of final containers and their labelling and packaging. Procedures should be specified for the storage of unlabelled containers in order to prevent confusion and to ensure satisfactory storage conditions. Special attention should be paid to the storage of heat labile or photosensitive products. Storage temperatures should be specified.
64. For each stage of production, the yield of product should be reconciled with that expected from that process. Any significant discrepancies should be investigated.

Quality control

65. In-process controls play a specially important role in ensuring the consistency of the quality of biological medicinal products. Those controls which are crucial for the quality (e.g. virus removal) but which cannot be carried out on the finished product, should be performed at an appropriate stage of production.
66. It may be necessary to retain samples of intermediate products in sufficient amount and under appropriate storage conditions to allow repetition or confirmation of a batch control.
67. There may be a requirement for the continuous monitoring of data during a production process, for example monitoring of physical parameters during fermentation.
68. Continuous culture of biological products is a common practice and special consideration needs to be given to the quality control requirements arising from this type of production method.

Annex 6
Manufacture of Medicinal Gases

Principle

Gases which fulfil the definition of medicinal product of Directive 2001/83/EC or Directive 2001/82/EC (hereinafter, medicinal gases) are subject to the requirements laid down in these Directives, 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 should 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 should comply with the Basic Requirements of this guide (Part II), with the relevant part of this Annex, and with the other Annexes of the guide if relevant.

Manufacture of medicinal gases should comply with the Basic Requirements of this guide (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) should be considered as belonging to the pharmaceutical field. This should 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 (as for example in an air separation plant).

1. The processes corresponding to these two methods of manufacturing active substance gases should 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 should 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 on-going 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) should be continuously monitored for quality. The results of this monitoring should be kept in a manner permitting trend evaluation.

3. In addition:

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

(b) filling of active substance gases into cylinders or into mobile cryogenic vessels should 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

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 should also apply to cylinders bundles (except storage and transportation under cover).

Personnel

5. All personnel involved in manufacture and distribution of medicinal gases should receive an appropriate GMP training specifically applying to this type of products. They should be aware of the critically important aspects and potential hazards for patients from these products. The training programs should include the tanker lorries drivers.

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

Premises and equipment

Premises

7. Cylinders and mobile cryogenic vessels should be checked, prepared, filled and stored in separate areas from non-medicinal gases, and there should 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 should provide sufficient space for manufacturing, testing and storage operations in order to prevent any risk of mix-up. Premises should 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 should be stored under cover, protected from adverse weather conditions. Filled cylinders/mobile cryogenic vessels should 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 should be provided as required by the Marketing Authorisation (e.g. for gas mixtures where phase separation occurs on freezing).

Equipment

11. Equipment should be designed to ensure the correct gas is filled into the correct container. There should normally be no cross connections between pipelines carrying different gases. If cross connections are needed (e.g. filling equipment of mixtures), qualification should ensure that there is no risk of cross contamination between the different gases. In addition, the manifolds should 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 should 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 should 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 should 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 should 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 should be at least equal to the required quality of the medicinal gas and GMP standards should be maintained. Filling should then be carried out by campaigns.
15. Repair and maintenance operations (including cleaning and purging) of equipment, should not adversely affect the quality of medicinal gases. In particular, procedures should describe the measures to be taken after repair and maintenance operations involving breaches of the system’s integrity. Specifically it should 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 should be maintained.

16. A procedure should 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 should include analytical testing. 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 should 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 should be maintained for each batch of gas intended to be delivered into hospital tanks. These records should, 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;

Production

Transfers and deliveries of cryogenic and liquefied gas

19. The transfers of cryogenic or liquefied gases from primary storage, including controls before transfers, should be in accordance with validated procedures designed to avoid the possibility of contamination. Transfer lines should be equipped with non-return valves or other suitable alternatives. Flexible connections, coupling hoses and connectors should be flushed with the relevant gas before use.
20. The transfer hoses used to fill tanks and tankers should be equipped with product-specific connections. The use of adaptors allowing the connection of tanks and tankers not dedicated to the same gases should 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) should be determined, controlled according to specifications and approved for filling.
23. In the case of continuous processes as those mentioned in 'Principle', there should be adequate in-process controls to ensure that the gas complies with specifications.
24. Cylinders, mobile cryogenic vessels and valves should conform to appropriate technical specifications and any relevant requirements of the Marketing Authorisation. They should be dedicated to a single medicinal gas or to a given mixture of medicinal gases. Cylinders should be colour-coded according to relevant standards. They should 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 should be checked before first use in production, and should be properly maintained. Where CE marked medical devices are used, the maintenance should address the medical device manufacturer's instructions.
26. Checks and maintenance operations should not affect the quality and the safety of the medicinal product. The water used for the hydrostatic pressure testing carried out on cylinders should be at least of drinking quality.
27. As part of the checks and maintenance operations, cylinders should be subject to an internal visual inspection before fitting the valve, to make sure they are not contaminated with water or other contaminants. This should 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 should 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 should 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 should only be carried out by approved subcontractors, and contracts including technical agreements should be established. Subcontractors should be audited to ensure that appropriate standards are maintained.

29. There should be a system to ensure the traceability of cylinders, mobile cryogenic vessels and valves.

30. Checks to be performed before filling should 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 should be checked, and if the valve is shown not to function properly the cylinder should 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 should 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 should 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 should be defined for filling operations.

32. Cylinders that have been returned for refilling should 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 should include evacuation and/or purging operations, should be validated. Note: For compressed gases, a maximum theoretical impurity of 500 ppm v/v should 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 should 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 should be prepared using a validated method.

34. There should be appropriate checks to ensure that each cylinder/mobile cryogenic vessel has been properly filled.

35. Each filled cylinder should be tested for leaks using an appropriate method, prior to fitting the tamper evident seal (see section 36). The test method should not introduce any contaminant into the valve outlet and, if applicable, should be performed after any quality sample is taken.

36. After filling, cylinders valves should be fitted with covers to protect the outlets from contamination. Cylinders and mobile cryogenic vessels should be fitted with tamper-evident seals.

37. Each cylinder or mobile cryogenic vessel should 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 should 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) should 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 should 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 should 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 should 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 should 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 should follow the same principles as single gases when continuous in-line testing of the mixture to be filled is performed. Premixed gases should 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 should 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 should include a test for assay and identity on each vessel. Testing by batches should 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 should be demonstrated that the specification of the gas in the vessels is maintained over the successive refillings.
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 should 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 1.013 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 Directives 2001/83/EC and 2001/82/EC).

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 the 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 1.013 bar, by opening the container / system to atmosphere.

Annex 7
Manufacture of Herbal Medicinal Products

Principle

Because of their often complex and variable nature, 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 product[1] can be a medicinal plant, a herbal substance[2] or a herbal preparation[1] . The herbal substance shall be of suitable quality and supporting data should 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 HMPC guidance document: "Guideline on Good Agricultural and Collection Practice for starting materials of herbal origin".

This Annex applies to all herbal starting materials: medicinal plants, herbal substances or herbal preparations.

[1] Throughout the annex and unless otherwise specified, the term "herbal medicinal product/ preparation" includes "traditional herbal medicinal product/ preparation".

[2] 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 application of Good Practices to the manufacture of herbal medicinal products[3].

Activity	**Good Agricultural and Collection Practice (GACP)**[4]	**Part II of the GMP Guide†**	**Part I of the GMP Guide†**
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 applied.

* Manufacturers should ensure that these steps are carried out in accordance with the marketing authorisation/registration. For those initial steps that take place in the field, as justified in the marketing authorisation/registration, the standards of 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 should be regarded as exceptional and justified in the relevant marketing authorisation/ registration documentation. For activities carried out in the field, appropriate documentation, control, and validation according to the GMP principles should be assured. Regulatory authorities may carry out GMP inspections of these activities in order to assess compliance.

3 This table expands in detail the herbal section of Table 1 in part II of the GMP Guide.
4 as published by the European Medicines Agency EMEA

Premises & Equipment

Storage areas

1. Herbal substances should be stored in separate areas. The storage area should be equipped in such a way as to give protection against the entry of insects or other animals, especially rodents. Effective measures should be taken to prevent the spread of any such animals and micro-organisms brought in with the herbal substance, to prevent fermentation or mould growth and to prevent cross-contamination. Different enclosed areas should be used to quarantine incoming herbal substances and for the approved herbal substances.
2. The storage area should be well aerated and the containers should be located in such a way so as to allow free circulation of air.
3. Special attention should 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 conditions should be provided and monitored.

Production area

5. Specific provisions should 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 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 should be made available. Audit trails for the active substance are fundamental to the quality of the starting material. The manufacturer should ensure that the suppliers of the herbal substance/preparation are in compliance with Good Agricultural and Collection Practice.
8. To fulfil the specification requirements described in the basic requirements of the Guide (chapter 4), documentation for herbal substances/preparations should 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 should 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, possible radioactive contamination etc.);
— which part(s) of the plant is/are used;
— when a dried plant is used, the drying system should be specified;
— a description of the herbal substance and its macro and microscopic examination;
— suitable identification tests including, where appropriate, identification tests for constituents with known therapeutic activity, or markers. Specific distinctive tests are required where an herbal substance is liable to be adulterated/ substituted. A reference authentic specimen should 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 European Pharmacopoeia methods 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 should be documented. Specifications and procedures should be available and should include details of process, tests and limits for residues.

Processing instructions

9. The processing instructions should 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 should 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 should 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 an herbal preparation, instructions should 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 should be carried out with special care by personnel with particular expertise. Each batch should 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 should 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 recognise 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 should 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 Ph. Eur. 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 nonrepresentative 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, items 6.11. to 6.14. This annex gives additional guidance on the sampling of starting and packaging materials.

Personnel

1. Personnel who take samples should receive initial and on-going regular training in the disciplines relevant to correct sampling. This training should include:
   - sampling plans,
   - written sampling procedures,
   - the techniques and equipment for sampling,
   - the risks 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 permissible 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 should 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 should be determined statistically and specified in a sampling plan. The number of individual samples which may be blended to form a composite sample should 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 should 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 should 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 should normally be effectively ventilated with filtered air.
2. Tanks, containers, pipework and pumps should be designed and installed so that they may be readily cleaned and if necessary sanitised. In particular, equipment design should include a minimum of dead-legs or sites where residues can accumulate and promote microbial proliferation.
3. The use of glass apparatus should be avoided wherever possible. High quality stainless steel is often the material of choice for parts coming into contact with product.

Production

4. The chemical and microbiological quality of water used in production should be specified and monitored. Care should 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 should be followed to ensure that the sanitising agent has been effectively removed.
5. The quality of materials received in bulk tankers should be checked before they are transferred to bulk storage tanks.
6. Care should 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, should not enter the areas where products or clean containers are exposed.
8. Care should be taken to maintain the homogeneity of mixtures, suspensions, etc. during filling. Mixing and filling processes should be validated. Special care should 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 should 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 form of product. It should 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 should be carried out as far as possible in a closed system.
3. Where products or clean components are exposed, the area should be fed with filtered air, should comply with the requirements of at least a Grade D environment and should 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 should recognise this. Auditing the Quality Assurance system of the valve manufacturer is of particular importance.
5. All fluids (e.g. liquid or gaseous propellants) should be filtered to remove particles greater than 0.2 micron. An additional filtration where possible immediately before filling is desirable.
6. Containers and valves should be cleaned using a validated procedure appropriate 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 should be kept in clean, closed containers and precautions taken not to introduce contamination during subsequent handling, e.g. taking samples. Containers should be fed to the filling line in a clean condition or cleaned on line immediately before filling.

7. Precautions should 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 should ensure the absence of undue leakage. Any leakage test should 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 fulfill 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. All personnel should have appropriate qualifications, level of access and defined responsibilities to carry out their assigned duties.

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 up to date listing of all relevant systems and their GMP functionality (inventory) should be available. For critical systems an up to date 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 compliant with GMP. 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:

(i) 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.

(ii) 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 authorisation 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) Requirement for re-commissioning.
    e)

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 of 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 nonirradiated 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 (31.) and appropriate design of premises (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
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 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.

Notes

Non-investigational medicinal product[1] 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 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 authorisation 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 this provision, 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.

[1] Further information can be found in the European Commission's Guidance on Investigational Medicinal Products (IMPs) and other Medicinal Products used in Clinical Trials

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.

Investigational medicinal product

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product 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.

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 principal investigator.

Manufacturer/importer of Investigational Medicinal Products

Any person engaged in activities for which the authorisation referred to in Article 13(1) of Directive 2001/20/EC 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 on-going clinical trials should be investigated and documented[2].

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 and finished product;
   - 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.

   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 different Qualified Persons, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations.

[2] 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

Manufacturing Formulae and Processing Instructions

10. 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.
11. 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 Directive 2003/94/EC.

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. Parameters identified and controlled 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 product

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 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 Directive 2003/94/EC. 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 Article 14 of Directive 2001/20/EC, 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 health care 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 9(2) of Directive 2001/20/EC. 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 permits, 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 13.3 of Directive 2001/20/EC 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) i) Product manufactured within EU but not subject to an EU marketing authorisation: the duties are laid down in article 13.3(a) of Directive 2001/20/EC.

    (b) ii) Product sourced from the open market within EU in accordance with Article 80(b) of Directive 2001/83/EC 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 13.3(b) of Directive 2001/20/EC. 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 40).

    (d) For imported comparator products where adequate assurance cannot be obtained in order to certify that each batch has been manufactured to equivalent standards of Good Manufacturing Practice, the duty of the Qualified Person is defined in article 13.3(c) of Directive 2001/20/EC.

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 9(2) of Directive 2001/20/EC. 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[3] 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 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.

[3] A harmonised format for batch certification to facilitate movement between Member States is provided in attachment 3.

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 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 (§26 TO 30)

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; Particulars a[4] to k
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; PRIMARY PACKAGE Where primary and secondary packaging remain together throughout (§29)[5]
e) the trial subject identification number/treatment number and where relevant, the visit number; a[6] b[7] c d e
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.

GENERAL CASE

For both the primary and secondary packaging (§2[6])

Particulars a[4] to k

PRIMARY PACKAGE

Where primary and secondary packaging remain together throughout (§29)5

a6 b7 c d e

PRIMARY PACKAGE

Blisters or small packaging units (§30)5

a6 b7,8 c d e

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

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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.

GENERAL CASE For both the primary and secondary packaging (§26)

Particulars a[4] to k

PRIMARY PACKAGE Where primary and secondary packaging remain together throughout (§29)[5]

a[6] b[7] c d e

PRIMARY PACKAGE

Blisters or small packaging units (§30)[5]

a[6] b[7,8] c d e

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).

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Table 2: BATCH RELEASE OF PRODUCTS

Table 2: BATCH RELEASE OF PRODUCTS

ELEMENTS TO BE TAKEN INTO ACCOUNT(3)	PRODUCT AVAILABLE IN THE EU		PRODUCT IMPORTED FROM THIRD COUNTRIES		
	Product manufactured in EU without MA	Product with MA and available on EU market	Product without any EU MA	Product with a EU MA	Comparator where documentation certifying that each batch has been manufactured in conditions at least equivalent to those laid down in Directive 2003/94/EC cannot be obtained
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: Directive 2003/94/EC, or GMP standards at least equivalent to those laid down in Directive 2003/94/EC.	Yes -		Yes (2)		
c) Documentation showing that each batch has been released within the EU according to EU GMP requirements (see Directive 2001/83/EC, article 51), or documentation showing that the product is available on the EU market and has been procured in accordance with article 80(b) of Directive 2001/83/EC.		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 Directive 2001/83/EC, article 51b), or the Product Specification File, the Order, article 9.2 submission to the regulatory authorities.			-	Yes	-
Where these analyses and tests are not performed in the EU, this should be justified and the QP must certify that they have been carried out in accordance with GMP standards at least equivalent to those laid down in Directive 2003/94/EC.			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: Directive 2003/94/EC, or GMP standards at least equivalent to those laid down in Directive 2003/94/EC.	Yes -		Yes (2)		

ATTACHMENT 3

[LETTERHEAD OF MANUFACTURER] Content of the Batch Certificate Referred to in Art. 13.3 Directive 2001/20/EC

(1) Name(s) of product(s)/product identifier(s) as referred to in the clinical trial application, where applicable.
(2) EudraCT No(s) and sponsor protocol code number, when available.
(3) 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.
(4) Dosage form (pharmaceutical form)
(5) Package size (contents of container) and type (e.g. vials, bottles, blisters).
(6) Lot/batch number
(7) Expiry/retest/use by date
(8) Name and address of manufacturer where the Qualified Person issuing the certificate is located.
(9) Manufacturing Authorisation number for the site listed under item 8.
(10) Comments/remarks
(11) Any additional information considered relevant by the QP.
(12) Certification statement.
(13) "I hereby certify that this batch complies with the requirements of Article 13.3 of Directive 2001/20/EC "
(14) Name of the QP signing the certificate
(15) Signature
(16) 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 13.3(a), (b) or (c) of Directive 2001/20/EC have been complied with and documented in accordance with Art. 13.4 of the same Directive. According to Directive 2001/20/EC a batch of investigational medicinal product shall not have to undergo further checks in relation to the provisions of article 13.3(a), (b) or (c) of the same directive 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 Plasma

Contents

GLOSSARY

Blood

Blood, as referred to in Directive 2002/98/EC (Art. 3a), 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 Directive 2002/98/EC (Art. 3b), 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 Directive 2002/98/EC (Art. 3e), 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 Directive 2002/98/EC (Art. 3c), 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

Good practice guidelines give interpretation on the Community standards and specifications defined for quality systems in blood establishments established in the Annex of Directive 2005/62/EC.[1]

[1] At the time of publication of this Annex adoption of the Good Practice guidelines by the European Commission was still pending

Medicinal products derived from human blood or human plasma

Medicinal products derived from human blood or human plasma, as referred to in Directive 2001/83/EC (Art. 1 No. 10), are medicinal products based on blood constituents which are prepared industrially by public or private establishments.

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 Directive 2001/83/EC (Annex I, 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 directive 2005/62/EC, "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 Directive 2001/83/EC (Art. 48).

Responsible Person (RP)

The responsible person is the person referred to in Directive 2002/98/EC (Art. 9).

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

1.1 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 Directive 2003/63/EC, 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 Commission Directive 2003/94/EC and the EU Guidelines on GMP published by the European Commission) as well as the relevant marketing authorisation (Directive 2001/83/EC, Art. 46, 51). They are considered to be biological medicinal products and the starting materials include biological substances, such as cells or fluids (including blood or plasma) of human origin (Directive 2001/83/EC Annex I 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 Directive 2002/98/EC 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 of Directive 2005/62/EC and interpreted in the Good Practice guidelines referred to in Article 2 (2) of Directive 2005/62/EC. Furthermore, the requirements of Directive 2005/61/EC 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 (Directive 2001/83/EC, Annex 1, Part III No. 1.1.b).

2.3 Starting material 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 Commission Directive 2005/62/EC (Recital 6; Article 2(3)), the traceability and serious adverse reaction and serious adverse event notification requirements as set out in Commission Directive 2005/61/EC (Recital 5; Article 7), 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 Commission Directive 2005/62/EC, the traceability requirements and notification of serious adverse reactions and events set out in Commission Directive 2005/61/EC and the relevant WHO guidelines and recommendations as listed in the addendum

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 Directive 2001/83/EC 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 material 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 Directive 2005/61/EC for traceability up to and including the delivery of plasma to the fractionation plant, and to Directive 2005/62/EC 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 Directive 2005/62/EC, are authorised by a national competent authority and are subject to regular inspections as referred to in Directive 2002/98/EC. Third country contract fractionation programs have to be notified to the competent EU authority by the manufacturer as referred to in Directive 2001/83/EC.

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
- traceability and post donation / collection information (including adverse events).

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 look back units2
- 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 4 of Directive 2005/61/EC and Article 14 of Directive 2002/98/EC3 .

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 final 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 II part A and Annex III part A of Directive 2005/61/EC, and other relevant information found subsequent to donor acceptance or release of the plasma, e.g. look back information 4 (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 authority5 responsible for the fractionation plant/manufacturer.

4.6 The notification procedure as described in 4.5 also applies when an inspection of a blood establishment by a competent authority leads to a withdrawal of an existing licence/certificate/ approval.

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.6

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 EU-GMP Guide. 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 EU-GMP Guide.

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

3 Both Directives are linked to Article 109 of Directive 2001/83/EC by defining specific rules for medicinal products derived from human blood or plasma

4 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

5 as referred to in Directive 2001/83/EC

6 Current version at date of publication: CPMP/BWP/269/95

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 Agency7 .

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 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.

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 should be in place, that take this risk into consideration.

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 8. 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 final 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).

Addendum

A) Member States should implement the following Directives and guidelines:

1. for collection and testing of blood and blood components:

Directive/Guidelines	**Title**	**Scope**
Directive 2002/98/EC of the European Parliament and of the Council	Setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components, amending Directive 2001/83/EC.	Art.2 Defines standards of quality and safety for the collection and testing of human blood and blood components, whatever their intended purpose, and for their processing, storage and distribution when intended for transfusion.
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).
Commission Directive 2005/61/EC	Implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events.	Defines traceability requirements for blood establishments, donors, blood and blood components, and for the final destination of each unit, whatever the intended purpose. It further defines the reporting requirements in the event of serious adverse events and reactions.
Commission Directive 2005/62/EC	Implementing Directive 2002/98/EC of the European Parliament and of the Council as regards Community standards and specifications relating to a quality system for blood establishments.	Defines the implementation of quality system standards and specifications as referred to in article 47 of Directive 2001/83/EC.

2. for collection and regulatory submission of data/information for plasma for fractionation:

Directive/Guidelines	**Title**	**Scope**
Directive 2001/83/EC of the European Parliament and the Council	On the Community Code relating to medicinal products for human use.	Art. 2 Medicinal products for human use intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, covering medicinal products derived from human blood or human plasma.
Commission Directive 2003/63/EC	Amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use; Amending the Annex on documentation of medicinal products	
Commission 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	Art. 1 Principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
EU Guidelines on Good Manufacturing Practice	Giving interpretation on the principles and guidelines on GMP	
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	
(Council of Europe) Guide to the Preparation, use and quality assurance of blood components WHO Recommendations for the production, control and regulation of human plasma for fractination. 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 revisions of these documents for current guidance.

Annex 15:
Qualification and Validation

Principle

This Annex describes the principles of qualification and validation which are applicable to the facilities, equipment, utilities and processes used for the manufacture of medicinal products and may also be used as supplementary optional guidance for active substances without introduction of additional requirements to EudraLex, Volume 4, Part II. It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process. Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed. Computerised systems used for the manufacture of medicinal products should also be validated according to the requirements of Annex 11. The relevant concepts and guidance presented in ICH Q8, Q9, Q10 and Q11 should also be taken into account.

General

A quality risk management approach should be applied throughout the lifecycle of a medicinal product. As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes. Retrospective validation is no longer considered an acceptable approach. Data supporting qualification and/or validation studies which were obtained from sources outside of the manufacturers own programmes may be used provided that this approach has been justified and that there is adequate assurance that controls were in place throughout the acquisition of such data.

1. ORGANISING AND PLANNING FOR QUALIFICATION AND VALIDATION

1.1 All qualification and validation activities should be planned and take the life cycle of facilities, equipment, utilities, process and product into consideration.

1.2 Qualification and validation activities should only be performed by suitably trained personnel who follow approved procedures.

1.3 Qualification/validation personnel should report as defined in the pharmaceutical quality system although this may not necessarily be to a quality management or a quality assurance function. However, there should be appropriate quality oversight over the whole validation life cycle.

1.4 The key elements of the site qualification and validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent document.

1.5 The VMP or equivalent document should define the qualification/validation system and include or reference information on at least the following:

i. Qualification and Validation policy;

ii. The organisational structure including roles and responsibilities for qualification and validation activities;

iii. Summary of the facilities, equipment, systems, processes on site and the qualification and validation status;
iv. Change control and deviation management for qualification and validation;
v. Guidance on developing acceptance criteria;
vi. References to existing documents;
vii. The qualification and validation strategy, including requalification, where applicable.

1.6 For large and complex projects, planning takes on added importance and separate validation plans may enhance clarity

1.7 A quality risk management approach should be used for qualification and validation activities. In light of increased knowledge and understanding from any changes during the project phase or during commercial production, the risk assessments should be repeated, as required. The way in which risk assessments are used to support qualification and validation activities should be clearly documented.

1.8 Appropriate checks should be incorporated into qualification and validation work to ensure the integrity of all data obtained.

2. DOCUMENTATION, INCLUDING VMP

2.1 Good documentation practices are important to support knowledge management throughout the product lifecycle.

2.2 All documents generated during qualification and validation should be approved and authorised by appropriate personnel as defined in the pharmaceutical quality system.

2.3 The inter-relationship between documents in complex validation projects should be clearly defined.

2.4 Validation protocols should be prepared which defines the critical systems, attributes and parameters and the associated acceptance criteria.

2.5 Qualification documents may be combined together, where appropriate, e.g. installation qualification (IQ) and operational qualification (OQ).

2.6 Where validation protocols and other documentation are supplied by a third party providing validation services, appropriate personnel at the manufacturing site should confirm suitability and compliance with internal procedures before approval. Vendor protocols may be supplemented by additional documentation/test protocols before use.

2.7 Any significant changes to the approved protocol during execution, e.g. acceptance criteria, operating parameters etc., should be documented as a deviation and be scientifically justified.

2.8 Results which fail to meet the pre-defined acceptance criteria should be recorded as a deviation and be fully investigated according to local procedures. Any implications for the validation should be discussed in the report

2.9 The review and conclusions of the validation should be reported and the results obtained summarised against the acceptance criteria. Any subsequent changes to

acceptance criteria should be scientifically justified and a final recommendation made as to the outcome of the validation.

2.10 A formal release for the next stage in the qualification and validation process should be authorised by the relevant responsible personnel either as part of the validation report approval or as a separate summary document. Conditional approval to proceed to the next qualification stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity.

3. QUALIFICATION STAGES FOR EQUIPMENT, FACILITIES, UTILITIES AND SYSTEMS.

3.1 Qualification activities should consider all stages from initial development of the user requirements specification through to the end of use of the equipment, facility, utility or system. The main stages and some suggested criteria (although this depends on individual project circumstances and may be different) which could be included in each stage are indicated below:

User requirements specification (URS)

3.2 The specification for equipment, facilities, utilities or systems should be defined in a URS and/or a functional specification. The essential elements of quality need to be built in at this stage and any GMP risks mitigated to an acceptable level. The URS should be a point of reference throughout the validation life cycle.

Design qualification (DQ)

3.3 The next element in the qualification of equipment, facilities, utilities, or systems is DQ where the compliance of the design with GMP should be demonstrated and documented. The requirements of the user requirements specification should be verified during the design qualification.

Factory acceptance testing (FAT) /Site acceptance testing (SAT)

3.4 Equipment, especially if incorporating novel or complex technology, may be evaluated, if applicable, at the vendor prior to delivery.

3.5 Prior to installation, equipment should be confirmed to comply with the URS/ functional specification at the vendor site, if applicable.

3.6 Where appropriate and justified, documentation review and some tests could be performed at the FAT or other stages without the need to repeat on site at IQ/OQ if it can be shown that the functionality is not affected by the transport and installation.

3.7 FAT may be supplemented by the execution of a SAT following the receipt of equipment at the manufacturing site.

Installation qualification (IQ)

3.8 IQ should be performed on equipment, facilities, utilities, or systems.

3.9 IQ should include, but is not limited to the following:

i. Verification of the correct installation of components, instrumentation, equipment, pipe work and services against the engineering drawings and specifications;
ii. Verification of the correct installation against pre-defined criteria;
iii. Collection and collation of supplier operating and working instructions and maintenance requirements;
iv. Calibration of instrumentation;
v. Verification of the materials of construction.

Operational qualification (OQ)

3.10 OQ normally follows IQ but depending on the complexity of the equipment, it may be performed as a combined Installation/Operation Qualification (IOQ).

3.11 OQ should include but is not limited to the following:
i. Tests that have been developed from the knowledge of processes, systems and equipment to ensure the system is operating as designed;
ii. Tests to confirm upper and lower operating limits, and /or "worst case" conditions.

3.12 The completion of a successful OQ should allow the finalisation of standard operating and cleaning procedures, operator training and preventative maintenance requirements. Performance qualification (PQ)

3.13 PQ should normally follow the successful completion of IQ and OQ. However, it may in some cases be appropriate to perform it in conjunction with OQ or Process Validation.

3.14 PQ should include, but is not limited to the following:
i. Tests, using production materials, qualified substitutes or simulated product proven to have equivalent behaviour under normal operating conditions with worst case batch sizes. The frequency of sampling used to confirm process control should be justified;
ii. Tests should cover the operating range of the intended process, unless documented evidence from the development phases confirming the operational ranges is available.

4. RE-QUALIFICATION

4.1 Equipment, facilities, utilities and systems should be evaluated at an appropriate frequency to confirm that they remain in a state of control.

4.2 Where re-qualification is necessary and performed at a specific time period, the period should be justified and the criteria for evaluation defined. Furthermore, the possibility of small changes over time should be assessed.

5. PROCESS VALIDATION

General

5.1 The requirements and principles outlined in this section are applicable to the manufacture of all pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes, site transfers and

ongoing process verification. It is implicit in this annex that a robust product development process is in place to enable successful process validation.

5.2 Section 5 should be used in conjunction with the current EMA guideline on Process Validation.

5.2.1 The guideline on Process Validation is intended to provide guidance on the information and data to be provided in the regulatory submission only. However GMP requirements for process validation continue throughout the lifecycle of the process

5.2.2 This approach should be applied to link product and process development. It will ensure validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production.

5.3 Manufacturing processes may be developed using a traditional approach or a continuous verification approach. However, irrespective of the approach used, processes must be shown to be robust and ensure consistent product quality before any product is released to the market. Manufacturing processes using the traditional approach should undergo a prospective validation programme, wherever possible, prior to certification of the product. Retrospective validation is no longer an acceptable approach.

5.4 Process validation of new products should cover all intended marketed strengths and sites of manufacture. Bracketing could be justified for new products based on extensive process knowledge from the development stage in conjunction with an appropriate ongoing verification programme.

5.5 For process validation of products which are transferred from one site to another or within the same site, the number of validation batches could be reduced by the use of a bracketing approach. However, existing product knowledge, including the content of the previous validation, should be available. Different strengths, batch sizes and pack sizes/container types may also use a bracketing approach, if justified.

5.6 For the site transfer of legacy products, the manufacturing process and controls must comply with the marketing authorisation and meet current standards for marketing authorisation for that product type. If necessary, variations to the marketing authorisation should be submitted.

5.7 Process validation should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process. The basis by which process parameters and quality attributes were identified as being critical or non-critical should be clearly documented, taking into account the results of any risk assessment activities.

5.8 Normally batches manufactured for process validation should be the same size as the intended commercial scale batches and the use of any other batch sizes should be justified or specified in other sections of EudraLex, Volume 4.

5.9 Equipment, facilities, utilities and systems used for process validation should be qualified. Test methods should be validated for their intended use.

5.10 For all products irrespective of the approach used, process knowledge from development studies or other sources should be accessible to the manufacturing site, unless otherwise justified, and be the basis for validation activities.

5.11 For process validation batches, production, development, or other site transfer personnel may be involved. Batches should only be manufactured by trained personnel in accordance with GMP using approved documentation. It is expected that production personnel are involved in the manufacture of validation batches to facilitate product understanding.

5.12 The suppliers of critical starting and packaging materials should be qualified prior to the manufacture of validation batches; otherwise a justification based on the application of quality risk management principles should be documented.

5.13 It is especially important that the underlying process knowledge for the design space justification (if used) and for development of any mathematical models (if used) to confirm a process control strategy should be available.

5.14 Where validation batches are released to the market, this should be pre-defined. The conditions under which they are produced should fully comply with GMP, with the validation acceptance criteria, with any continuous process verification criteria (if used) and with the marketing authorisation or clinical trial authorisation.

5.15 For the process validation of investigational medicinal products (IMP), please refer to Annex 13.

Concurrent validation

5.16 In exceptional circumstances, where there is a strong benefit-risk ratio for the patient, it may be acceptable not to complete a validation programme before routine production starts and concurrent validation could be used. However, the decision to carry out concurrent validation must be justified, documented in the VMP for visibility and approved by authorised personnel.

5.17 Where a concurrent validation approach has been adopted, there should be sufficient data to support a conclusion that any given batch of product is uniform and meets the defined acceptance criteria. The results and conclusion should be formally documented and available to the Qualified Person prior to certification of the batch.

Traditional process validation

5.18 In the traditional approach, a number of batches of the finished product are manufactured under routine conditions to confirm reproducibility.

5.19 The number of batches manufactured and the number of samples taken should be based on quality risk management principles, allow the normal range of variation and trends to be established and provide sufficient data for evaluation. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.

5.20 Without prejudice to 5.19, it is generally considered acceptable that a minimum of three consecutive batches manufactured under routine conditions could

constitute a validation of the process. An alternative number of batches may be justified taking into account whether standard methods of manufacture are used and whether similar products or processes are already used at the site. An initial validation exercise with three batches may need to be supplemented with further data obtained from subsequent batches as part of an on-going process verification exercise.

5.21 A process validation protocol should be prepared which defines the critical process parameters (CPP), critical quality attributes (CQA) and the associated acceptance criteria which should be based on development data or documented process knowledge.

5.22 Process validation protocols should include, but are not limited to the following:

i. A short description of the process and a reference to the respective Master Batch Record;
ii. Functions and responsibilities;
iii. Summary of the CQAs to be investigated;
iv. Summary of CPPs and their associated limits;
v. Summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion;
vi. List of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with the calibration status;
vii. List of analytical methods and method validation, as appropriate.
viii. Proposed in-process controls with acceptance criteria and the reason(s) why each in-process control is selected;
ix. Additional testing to be carried out with acceptance criteria;
x. Sampling plan and the rationale behind it;
xi. Methods for recording and evaluating results;
xii. Process for release and certification of batches (if applicable).

Continuous process verification

5.23 For products developed by a quality by design approach, where it has been scientifically established during development that the established control strategy provides a high degree of assurance of product quality, then continuous process verification can be used as an alternative to traditional process validation.

5.24 The method by which the process will be verified should be defined. There should be a science based control strategy for the required attributes for incoming materials, critical quality attributes and critical process parameters to confirm product realisation. This should also include regular evaluation of the control strategy. Process Analytical Technology and multivariate statistical process control may be used as tools. Each manufacturer must determine and justify the number of batches necessary to demonstrate a high level of assurance that the process is capable of consistently delivering quality product.

5.25 The general principles laid down in 5.1 – 5.14 above still apply.

Hybrid approach

5.26 A hybrid of the traditional approach and continuous process verification could be used where there is a substantial amount of product and process knowledge and understanding which has been gained from manufacturing experience and historical batch data.

5.27 This approach may also be used for any validation activities after changes or during ongoing process verification even though the product was initially validated using a traditional approach.

Ongoing Process Verification during Lifecycle

5.28 Paragraphs 5.28-5.32 are applicable to all three approaches to process validation mentioned above, i.e. traditional, continuous and hybrid.

5.29 Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated.

5.30 The extent and frequency of ongoing process verification should be reviewed periodically. At any point throughout the product lifecycle, it may be appropriate to modify the requirements taking into account the current level of process understanding and process performance.

5.31 Ongoing process verification should be conducted under an approved protocol or equivalent documents and a corresponding report should be prepared to document the results obtained. Statistical tools should be used, where appropriate, to support any conclusions with regard to the variability and capability of a given process and ensure a state of control.

5.32 Ongoing process verification should be used throughout the product lifecycle to support the validated status of the product as documented in the Product Quality Review. Incremental changes over time should also be considered and the need for any additional actions, e.g. enhanced sampling, should be assessed.

6. VERIFICATION OF TRANSPORTATION

6.1 Finished medicinal products, investigational medicinal products, bulk product and samples should be transported from manufacturing sites in accordance with the conditions defined in the marketing authorisation, the approved label, product specification file or as justified by the manufacturer.

6.2 It is recognised that verification of transportation may be challenging due to the variable factors involved however, transportation routes should be clearly defined. Seasonal and other variations should also be considered during verification of transport

6.3 A risk assessment should be performed to consider the impact of variables in the transportation process other than those conditions which are continuously controlled or monitored, e.g. delays during transportation, failure of monitoring devices, topping up liquid nitrogen, product susceptibility and any other relevant factors.

6.4 Due to the variable conditions expected during transportation, continuous monitoring and recording of any critical environmental conditions to which the product may be subjected should be performed, unless otherwise justified.

7. VALIDATION OF PACKAGING

7.1 Variation in equipment processing parameters especially during primary packaging may have a significant impact on the integrity and correct functioning of the pack, e.g. blister strips, sachets and sterile components, therefore primary and secondary packaging equipment for finished and bulk products should be qualified.

7.2 Qualification of the equipment used for primary packing should be carried out at the minimum and maximum operating ranges defined for the critical process parameters such as temperature, machine speed and sealing pressure or for any other factors.

8. QUALIFICATION OF UTILITIES

8.1 The quality of steam, water, air, other gases etc. should be confirmed following installation using the qualification steps described in section 3 above.

8.2 The period and extent of qualification should reflect any seasonal variations, if applicable, and the intended use of the utility.

8.3 A risk assessment should be carried out where there may be direct contact with the product, e.g. heating, ventilation and air-conditioning (HVAC) systems, or indirect contact such as through heat exchangers to mitigate any risks of failure.

9. VALIDATION OF TEST METHODS

9.1 All analytical test methods used in qualification, validation or cleaning exercises should be validated with an appropriate detection and quantification limit, where necessary, as defined in Chapter 6 of the EudraLex, Volume 4, Part I.

9.2 Where microbial testing of product is carried out, the method should be validated to confirm that the product does not influence the recovery of microorganisms.

9.3 Where microbial testing of surfaces in clean rooms is carried out, validation should be performed on the test method to confirm that sanitising agents do not influence the recovery of microorganisms.

10. CLEANING VALIDATION

10.1 Cleaning validation should be performed in order to confirm the effectiveness of any cleaning procedure for all product contact equipment. Simulating agents may be used with appropriate scientific justification. Where similar types of equipment are grouped together, a justification of the specific equipment selected for cleaning validation is expected.

10.2 A visual check for cleanliness is an important part of the acceptance criteria for cleaning validation. It is not generally acceptable for this criterion alone to be used. Repeated cleaning and retesting until acceptable residue results are obtained is not considered an acceptable approach.

10.3 It is recognised that a cleaning validation programme may take some time to complete and validation with verification after each batch may be required for some products, e.g. investigational medicinal products. There should be sufficient data from the verification to support a conclusion that the equipment is clean and available for further use.

10.4 Validation should consider the level of automation in the cleaning process. Where an automatic process is used, the specified normal operating range of the utilities and equipment should be validated.

10.5 For all cleaning processes an assessment should be performed to determine the variable factors which influence cleaning effectiveness and performance, e.g. operators, the level of detail in procedures such as rinsing times etc. If variable factors have been identified, the worst case situations should be used as the basis for cleaning validation studies.

10.6 Limits for the carryover of product residues should be based on a toxicological evaluation[1]. The justification for the selected limits should be documented in a risk assessment which includes all the supporting references. Limits should be established for the removal of any cleaning agents used. Acceptance criteria should consider the potential cumulative effect of multiple items of equipment in the process equipment train.

10.6.1 Therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. A toxicological evaluation may therefore not be applicable in these circumstances.

10.6.2 If it is not feasible to test for specific product residues, other representative parameters may be selected, e.g. total organic carbon (TOC) and conductivity.

10.7 The risk presented by microbial and endotoxin contamination should be considered during the development of cleaning validation protocols.

10.8 The influence of the time between manufacture and cleaning and the time between cleaning and use should be taken into account to define dirty and clean hold times for the cleaning process.

10.9 Where campaign manufacture is carried out, the impact on the ease of cleaning at the end of the campaign should be considered and the maximum length of a campaign (in time and/or number of batches) should be the basis for cleaning validation exercises.

10.10 Where a worst case product approach is used as a cleaning validation model, a scientific rationale should be provided for the selection of the worst case product and the impact of new products to the site assessed. Criteria for determining the worst case may include solubility, cleanability, toxicity and potency.

[1]See EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities

10.11 Cleaning validation protocols should specify or reference the locations to be sampled, the rationale for the selection of these locations and define the acceptance criteria.

10.12 Sampling should be carried out by swabbing and/or rinsing or by other means depending on the production equipment. The sampling materials and method should not influence the result. Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used.

10.13 The cleaning procedure should be performed an appropriate number of times based on a risk assessment and meet the acceptance criteria in order to prove that the cleaning method is validated.

10.14 Where a cleaning process is ineffective or is not appropriate for some equipment, dedicated equipment or other appropriate measures should be used for each product as indicated in chapters 3 and 5 of EudraLex, Volume 4, Part I.

10.15 Where manual cleaning of equipment is performed, it is especially important that the effectiveness of the manual process should be confirmed at a justified frequency.

11. CHANGE CONTROL

11.1 The control of change is an important part of knowledge management and should be handled within the pharmaceutical quality system.

11.2 Written procedures should be in place to describe the actions to be taken if a planned change is proposed to a starting material, product component, process, equipment, premises, product range, method of production or testing, batch size, design space or any other change during the lifecycle that may affect product quality or reproducibility.

11.3 Where design space is used, the impact on changes to the design space should be considered against the registered design space within the marketing authorisation and the need for any regulatory actions assessed.

11.4 Quality risk management should be used to evaluate planned changes to determine the potential impact on product quality, pharmaceutical quality systems, documentation, validation, regulatory status, calibration, maintenance and on any other system to avoid unintended consequences and to plan for any necessary process validation, verification or requalification efforts.

11.5 Changes should be authorised and approved by the responsible persons or relevant functional personnel in accordance with the pharmaceutical quality system.

11.6 Supporting data, e.g. copies of documents, should be reviewed to confirm that the impact of the change has been demonstrated prior to final approval.

11.7 Following implementation, and, where appropriate, an evaluation of the effectiveness of change should be carried out to confirm that the change has been successful.

12. GLOSSARY

Definitions of terms relating to qualification and validation which are not given in other sections of the current EudraLex, Volume 4, are given below.

Bracketing approach. A science and risk based validation approach such that only batches on the extremes of certain predetermined and justified design factors, e.g. strength, batch size and/or pack size, are tested during process validation. The design assumes that validation of any intermediate levels is represented by validation of the extremes. Where a range of strengths is to be validated, bracketing could be applicable if the strengths are identical or very closely related in composition, e.g. for a tablet range made with different compression weights of a similar basic granulation or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells. Bracketing can be applied to different container sizes or different fills in the same container closure system.

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 to 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 reproducibly remove the previous product or cleaning agents used in the equipment below the scientifically set maximum allowable carryover level.

Cleaning verification. The gathering of evidence through chemical analysis after each batch/campaign to show that the residues of the previous product or cleaning agents have been reduced below the scientifically set maximum allowable carryover level.

Concurrent Validation. Validation carried out in exceptional circumstances, justified on the basis of significant patient benefit, where the validation protocol is executed concurrently with commercialisation of the validation batches.

Continuous process verification. An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. (ICH Q8)

Control Strategy. A planned set of controls derived from current product and process understanding that ensures 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)

Critical process parameter (CPP). A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8)

Critical quality attribute (CQA). A physical, chemical, biological or microbiological property or characteristic that should be within an approved limit, range or distribution to ensure the desired product quality. (ICH Q8)

Design qualification (DQ). The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.

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. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. (ICH Q8)

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.

Knowledge management. A systematic approach to acquire, analyse, store and disseminate information. (ICH Q10)

Lifecycle. All phases in the life of a product, equipment or facility from initial development or use through to discontinuation of use.

Ongoing Process Verification (also known as continued process verification). Documented evidence that the process remains in a state of control during commercial manufacture.

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 systems and equipment 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.

Product realisation. Achievement of a product with the quality attributes to meet the needs of patients, health care professionals and regulatory authorities and internal customer requirements. (ICH Q10)

Prospective Validation. Validation carried out before routine production of products intended for sale.

Quality by design. A systematic approach that begins with predefined objectives and emphasises product and process understanding and process control, based on sound science and quality risk management.

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

Simulated agents. 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.

State of control. A condition in which the set of controls consistently provides assurance of acceptable process performance and product quality.

Traditional approach. A product development approach where set points and operating ranges for process parameters are defined to ensure reproducibility.

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.

User requirements Specification (URS). The set of owner, user and engineering requirements necessary and sufficient to create a feasible design meeting the intended purpose of the system.

Annex 16
Certification by a Qualified Person and Batch Release

Scope

This Annex provides guidance on the certification by a Qualified Person (QP) and on batch release within the European Union (EU) of medicinal products for human or veterinary use holding a marketing authorisation (MA) or made for export. The principles of this guidance also apply to investigational medicinal products (IMP) for human use, subject to any difference in the legal provisions and more specific guidance published by the European Commission.

The relevant legislative requirements are provided in Article 51 of Directive 2001/83/EC, as amended, and in Article 55 of Directive 2001/82/EC. Notice is taken of the arrangements referred to in Article 51(2) of Directive 2001/83/EC, as amended, and Article 55(2) of Directive 2001/82/EC, e.g. Mutual Recognition Agreements (MRA).

This Annex does not address the "Official Control Authority Batch Release" which may be specified for certain blood and immunological products in accordance with Articles 109, 110, 113 and 114 of Directive 2001/83/EC, as amended, and Articles 81 and 82 of Directive 2001/82/EC. However, this Annex does apply to the QP certification and subsequent release of such batches.

The basic arrangements for batch release for a product are defined by its MA. Nothing in this Annex should be taken as overriding those arrangements.

General principles

The ultimate responsibility for the performance of a medicinal product over its lifetime, its safety, quality and efficacy, lies with the marketing authorisation holder (MAH).

However, the QP is responsible for ensuring that each individual batch has been manufactured and checked in compliance with laws in force in the Member State where certification takes place, in accordance with the requirements of the marketing authorisation (MA) and with Good Manufacturing Practice (GMP).

The process of batch release comprises of:

i. The checking of the manufacture and testing of the batch in accordance with defined release procedures.
ii. The certification of the finished product batch performed by a QP signifying that the batch is in compliance with GMP and the requirements of its MA. This represents the quality release of the batch.
iii. The transfer to saleable stock, and/or export of the finished batch of product which should take into account the certification performed by the QP. If this transfer is performed at a site other than that where certification takes place, then the arrangement should be documented in a written agreement between the sites.

The purpose of controlling batch release is notably to ensure that:

i. The batch has been manufactured and checked in accordance with the requirements of its MA.
ii. The batch has been manufactured and checked in accordance with the principles and guidelines of GM P.
iii. Any other relevant legal requirements are taken into account.

iv. In the event that a quality defect as referred to in Chapter 8 of EudraLex, Volume 4, Part I, needs to be investigated or a batch recalled, to ensure that any QPs involved in the certification or confirmation[1] and any relevant records are readily identifiable.

1. THE PROCESS OF CERTIFICATION

1.1 Each batch of finished product must be certified[2] by a QP within the EU before being released for sale or supply in the EU or for export. Certification can only be performed by a QP of the manufacturer and/or importer which are described in the MA.

1.2 Any QP involved in the certification, or confirmation of a batch must have detailed knowledge of the steps for which they are taking responsibility. The QPs should be able to prove their continuous training regarding the product type, production processes, technical advances and changes to GMP.

1.3 There may be several sites involved in the various stages of manufacture, importation, testing and storage of a batch before it undergoes certification. Regardless of how many sites are involved, the QP performing certification of the finished product must ensure that all necessary steps have been completed under accepted pharmaceutical quality systems to assure compliance of the batch with GMP, the MA and any other legal obligations in the Member State where certification is taking place.

1.4 For manufacturing steps performed at sites in the EU each manufacturing site must have at least one QP.

1.4.1 Where the site only undertakes partial manufacturing operations in relation to a batch, then a QP at that site must at least confirm that the operations undertaken by the site have been performed in accordance with GMP and the terms of the written agreement detailing the operations for which the site is responsible. If the QP is responsible for providing confirmation of compliance for those operations with the relevant MA, then the QP should have access to the necessary details of the MA.

1.4.2 The QP who performs certification of the finished product batch may assume full responsibility for all stages of manufacture of the batch or this responsibility may be shared with other QPs who have provided confirmation for specified steps in the manufacture and control of a batch. These could be other QPs who are operating under the same manufacturing authorisation (MIA) holder or QPs operating under different MIA holders.

[1] Information required for the confirmation, where QP responsibilities for the batch are being transferred between sites, is presented in Appendix I to this Annex.

[2] The contents of a batch certificate for medicinal products are presented in Appendix II to this Annex.

1.4.3 Any sharing of responsibilities amongst QPs in relation to compliance of a batch must be defined in a document formally agreed by all parties. This document should detail responsibility for assessment of the impact any deviation(s) has/have on compliance of the batch with GMP and the MA.

1.5 For medicinal products manufactured outside the EU, physical importation and certification are the final stages of manufacturing which precede the transfer to saleable stock of the batch.

1.5.1 The process of certification as described in Section 1 of this Annex, applies to all medicinal products intended to be released for the EU markets, or for export, irrespective of the complexity of the supply chain and the global locations of manufacturing sites involved.

1.5.2 In accordance with the principles described in Section 1.4 of this Annex, the QP certifying the finished medicinal product batch may take account of the confirmation by, and share defined responsibilities with, other QPs in relation to any manufacturing or importation operations taking place at other sites in the EU and other manufacturing authorisation holders defined in the relevant MA.

1.5.3 Conditions of storage and transport for the batch and the sample, if sent separately, should be taken into account by the QP before certification of a batch.

1.5.4 The QP certifying the finished product is responsible for ensuring that each finished medicinal product batch has been manufactured in accordance with GMP and the MA. Unless an MRA or similar agreement is in place between the EU and the exporting country, the QP is also responsible for ensuring that the finished medicinal product batch has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary to ensure the quality of medicinal products is in accordance with the requirements of the MA.

1.5.5 Sampling of imported product should be fully representative of the batch. Samples may either be taken after arrival in the EU, or be taken at the manufacturing site in the third country in accordance with a technically justified approach which is documented within the company's quality system. Responsibilities in relation to the sampling should be defined in a written agreement between the sites. Any samples taken outside the EU should be shipped under equivalent transport conditions as the batch that they represent.

1.5.6 Where sampling is performed at a third country manufacturing site, the technical justification should include a formal Quality Risk Management process to identify and manage any risks associated with this approach. This should be fully documented and include at least the following elements:

i. Audit of the manufacturing activity including any sampling activity at the third country site and evaluation of subsequent transportation

steps of both the batch and samples to ensure that the samples are representative of the imported batch.

ii. A comprehensive scientific study, including data to support any conclusions that samples taken in the third country are representative of the batch after importation.

This study should at least include:

- Description of the sampling process in the third country.
- Description of the transported conditions of the sample and the imported batch. Any differences should be justified.
- Comparative analysis of samples taken in the third country and samples taken after importation.
- Consideration of the time interval between sampling and importation of the batch and generation of data to support appropriate defined limits.

iii. Provision for random periodic analysis of samples taken after importation to justify ongoing reliance on samples taken in a third country.

iv. A review of any unexpected result or confirmed out of specification result. These may have implications for reliance on sampling performed at the third country manufacturing site and should be notified to the Supervisory Authority for the site where certification is performed. Such an occurrence should be regarded as a potential quality defect and investigated in line with the guidance in Chapter 8 of EudraLex, Volume 4, Part I.

1.5.7 Different imported finished product batches may originate from the same bulk product batch. The QPs certifying the different finished product batches may base their decision on the quality control testing of the first imported finished batch provided that a justification has been documented based on Quality Risk Management principles. This should take into account the provisions of paragraph 1.5.6 in relation to reliance on any samples taken in third countries. Evidence should be available to ensure that the integrity and identity of the imported finished product batch has been established through documented verification of at least the following:

i. Relevant requirements for storage of the bulk product prior to packaging have been satisfied;

ii. The finished product batch has been stored and transported under the required conditions;

iii. The consignment has remained secure and there is no evidence of tampering during storage or transportation;

iv. Correct identification of the product has been established;

v. The sample(s) tested are representative of all finished product batches derived from the bulk batch.

1.6 The QP must personally ensure that the following operational responsibilities are fulfilled prior to certification of a batch for release to market or for export:

i. Certification is permitted under the terms of the MIA.
ii. Any additional duties and requirements of national legislation are complied with.
iii. Certification is recorded in a register or equivalent document.

1.7 In addition, the QP has responsibility for ensuring points 1.7.1 to 1.7.21 are secured. These tasks may be delegated to appropriately trained personnel or third parties. It is recognised that the QP will need to rely on the pharmaceutical quality system and the QP should have on-going assurance that this reliance is well founded.

1.7.1 All activities associated with manufacture and testing of the medicinal product have been conducted in accordance with the principles and guidelines of GMP.

1.7.2 The entire supply chain of the active substance and medicinal product up to the stage of certification is documented and available for the QP. This should include the manufacturing sites of the starting materials and packaging materials for the medicinal product and any other materials deemed critical through a risk assessment of the manufacturing process. The document should preferably be in the format of a comprehensive diagram, where each party, including subcontractors of critical steps such as the sterilisation of components and equipment for aseptic processing, are included.

1.7.3 All audits of sites involved in the manufacture and the testing of the medicinal products and in the manufacture of the active substance have been carried out and that the audit reports are available to the QP performing the certification.

1.7.4 All sites of manufacture, analysis and certification are compliant with the terms of the MA for the intended territory.

1.7.5 All manufacturing activities and testing activities are consistent with those described in the MA.

1.7.6 The source and specifications of starting materials and packaging materials used in the batch are compliant with the MA. Supplier quality management systems are in place that ensure only materials of the required quality have been supplied.

1.7.7 For medicinal products that fall within the scope of Directive 2001/83/EC, as amended, or Directive 2001/82/EC, the active substances have been manufactured in accordance with GMP and, where required, distributed in accordance with Good Distribution Practice (GDP) for Active Substances.

1.7.8 The importation of active substances used in the manufacture of medicinal products for human use should comply with the requirements of Article 46(b) of Directive 2001/83/EC, as amended.

1.7.9 For medicinal products that fall within the scope of Directive 2001/83/EC, as amended, the excipients have been manufactured in accordance with the ascertained GMP referred to in Article 46 (f) of that Directive.

1.7.10 When relevant, the TSE (Transmissible Spongiform Encephalopathy) status of all materials used in batch manufacture is compliant with the terms of the MA.

1.7.11 All records are complete and endorsed by appropriate personnel. All required in-process controls and checks have been made.

1.7.12 All manufacturing and testing processes remain in the validated state. Personnel are trained and qualified as appropriate.

1.7.13 Finished product quality control (QC) test data complies with the Finished Product Specification described in the MA, or where authorised, the Real Time Release Testing programme.

1.7.14 Any regulatory post-marketing commitments relating to manufacture or testing of the product have been addressed. On-going stability data continues to support certification.

1.7.15 The impact of any change to product manufacturing or testing has been evaluated and any additional checks and tests are complete.

1.7.16 All investigations pertaining to the batch being certified (including out of specification and out of trend investigations) have been completed to a sufficient level to support certification.

1.7.17 Any on-going complaints, investigations or recalls do not negate the conditions for certification of the batch in question.

1.7.18 The required technical agreements are in place.

1.7.19 The self-inspection programme is active and current.

1.7.20 The appropriate arrangements for distribution and shipment are in place.

1.7.21 In the case of medicinal products for human use intended to be placed on the market in the Union, the safety features referred to in Article 54(o) of Directive 2001/83/EC, as amended, have been affixed to the packaging, where appropriate.

1.8 For certain products, special guidance may apply, such as EudraLex, Volume 4, Annex 2: Manufacture of Biological active substances and Medicinal Products for Human Use, and Annex 3: Manufacture of Radiopharmaceuticals.

1.9 In the case of parallel importation and parallel distribution any repackaging operation carried out on a batch which has already been released must be approved by the competent authority of the intended market.

1.9.1 Prior to certification of a repacked batch the QP should confirm compliance with national requirements for parallel importation and EU rules for parallel distribution.

1.9.2 The QP of the MIA holder, who is named responsible for the certification of the batch in the MA of the repackaged finished product, certifies that the repackaging has been performed in accordance with the relevant authorisation pertaining to the repackaged product and GMP.

1.10 Recording of QP certification.

1.10.1 The certification of a medicinal product is recorded by the QP in a register or equivalent document provided for that purpose. The record should show that each production batch satisfies the provisions of Article 51 of Directive 2001/83/EC, as amended, or Article 55 of Directive

2001/82/EC. The record must be kept up to date as operations are carried out and must remain at the disposal of the agents of the competent authority for the period specified in the provisions of the Member State concerned and in any event for at least five years

1.10.2 The control report referred to in Article 51 of Directive 2001/83/EC, as amended, or Article 55 of Directive 2001/82/EC or another proof for release to the market in question, based on an equivalent system, should be made available for the batch in order to be exempted from further controls when entering another Member State.

2. RELYING ON GMP ASSESSMENTS BY THIRD PARTIES, E.G. AUDITS

In some cases the QP will rely on the correct functioning of the pharmaceutical quality system of sites involved in the manufacture of the product and this may be derived from audits conducted by third parties.

2.1 Relying on assessment by third parties, e.g. audits, should be in accordance with Chapter 7 of the GMP Guide in order to appropriately define, agree and control any outsourced activity.

2.2 Special focus should be given to the approval of audit reports:

i. The audit report should address general GMP requirements, as for example the quality management system, all relevant production and quality control procedures related to the supplied product, e.g. active substance manufacturing, quality control testing, primary packaging, etc. All audited areas should be accurately described resulting in a detailed report of the audit.

ii. It should be determined whether the manufacture and quality control of the active substance and medicinal product complies with GMP, or in case of manufacture in third countries, GMP at least equivalent to that referred to in Article 46 of Directive 2001/83/EC, as amended, or Article 50 of Directive 2001/82/EC.

iii. In case of outsourced activities compliance with the MA should be verified.

iv. The QP should ensure that a written final assessment and approval of third party audit reports have been made. The QP should have access to all documentation which facilitates review of the audit outcome and continued reliance on the outsourced activity.

v. Outsourced activities with critical impact on product quality should be defined in accordance with the principles of Quality Risk Management as described in Part III of EudraLex, Volume 4. According to this, the QP should be aware of the outcome of an audit with critical impact on the product quality before certifying the relevant batches.

vi. Repeated audits should be performed in accordance with the principles of Quality Risk Management.

3. HANDLING OF UNEXPECTED DEVIATIONS

Provided registered specifications for active substances, excipients, packaging materials and medicinal products are met, a QP may consider confirming compliance or certifying a batch where an unexpected deviation concerning the manufacturing process and/or the analytical control methods from details contained within the MA and/or GMP has occurred. The deviation should be thoroughly investigated and the root cause corrected. This may require the submission of a variation to the MA for the continued manufacture of the product.

3.1 The impact of the deviation should be assessed in accordance with a quality risk management process using an appropriate approach such as described in Part III of the GMP Guide. The quality risk management process should include the following;

i. Evaluation of the potential impact of the deviation on quality, safety or efficacy of the batch(es) concerned and conclusion that the impact is negligible.

ii. Consideration of the need to include the affected batch(es) in the ongoing stability programme.

iii. In the case of biological medicinal products, consideration that any deviations from the approved process can have an unexpected impact on safety and efficacy. Taking account that responsibilities may be shared between more than one QPs involved in the manufacture and control of a batch, the QP performing certification of a batch of medicinal product should be aware of and take into consideration any deviations which have the potential to impact compliance with GMP and/or compliance with the MA.

4. THE RELEASE OF A BATCH

4.1 Batches of medicinal products should only be released for sale or supply to the market after certification by a QP as described above. Until a batch is certified, it should remain at the site of manufacture or be shipped under quarantine to another site which has been approved for that purpose by the relevant Competent Authority.

4.2 Safeguards to ensure that uncertified batches are not transferred to saleable stock should be in place and may be physical in nature, e.g. the use of segregation and labelling or electronic in nature, e.g. the use of validated computerised systems. When uncertified batches are moved from one authorised site to another, the safeguards to prevent premature release should remain.

4.3 The steps necessary to notify QP certification to the site where the transfer to saleable stock is to take place should be defined within a technical agreement. Such notification by a QP to the site should be formal and unambiguous and should be subject to the requirements of Chapter 4 of EudraLex, Volume 4, Part I.

5. 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.

Certification of the finished product batch. The certification in a register or equivalent document by a QP, as defined in Article 51 of Directive 2001/83/EC, as amended, and Article 55 of Directive 2001/82/EC, and represents the quality release of the batch before the batch is released for sale or distribution.

Confirmation (Confirm and confirmed have equivalent meanings). A signed statement by a QP that a process or test has been conducted in accordance with GMP and the relevant marketing authorisation or clinical trial authorisation, product specification file and/or technical agreement, as applicable, as agreed in writing with the QP responsible for certifying the finished product batch before release. The QP providing a confirmation takes responsibility for those activities being confirmed.

Finished product batch. With reference to the control or test of the finished product, a finished medicinal product batch is described in Annex I, Part I, point 3.2.2.5, of Directive 2001/83/EC and Annex I, Part 2, section E, of Directive 2001/82/EC. In the context of this annex the term in particular denotes the batch of product in its final pack for release to the market.

Importer. The holder of the authorisation required by Article 40(3) of Directive 2001/83/EC, as amended, and Article 44(3) of Directive 2001/82/EC for importing medicinal products from third countries.

Qualified Person (QP). The person defined in Article 48 of Directive 2001/83/EC, as amended, and Article 52 of Directive 2001/82/EC.

Appendix I

Content of the confirmation of the partial manufacturing of a medicinal product

[LETTER HEAD OF MANUFACTURER WHO CARRIED OUT THE MANUFACTURING ACTIVITY]

1. Name of the product and description of the manufacturing stage (e.g. paracetamol 500 mg tablets, primary packaging into blister packs).
2. Batch number.
3. Name and address of the site carrying out the partial manufacturing.
4. Reference to the Technical Quality Agreement (in accordance with Chapter 7 of the Guide).
5. Confirmation statement. I hereby confirm that the manufacturing stages referred to in the Technical Quality Agreement have been carried out in full compliance with the GMP requirements of the EU and the terms described in the Agreement for ensuring compliance with the requirements of the Marketing Authorisation(s) as provided by [Contract Giver/manufacturer certifying and releasing the batch].
6. Name of the Qualified Person confirming the partial manufacturing.
7. Signature of Qualified Person confirming the partial manufacturing.
8. Date of signature.

Appendix II

Content of the Batch Certificate for Medicinal Products

[LETTER HEAD OF THE BATCH CERTIFYING AND RELEASING MANUFACTURER]

1. Name, strength/potency, dosage form and package size (identical to the text on the finished product package).
2. Batch number of the finished product.
3. Name of the destination country/countries of the batch, at least when within the EU.
4. Certification statement. I hereby certify that all the manufacturing stages of this batch of finished product have been carried out in full compliance with the GMP requirements of the EU and [when within the EU] with the requirements of the Marketing Authorisation(s) of the destination country/countries.
5. Name of the Qualified Person certifying the batch.
6. Signature of the Qualified Person certifying the batch.
7. Date of signature.

Annex 17
Real Time Release Testing and Parametric Release

1. Principle

1.1 Medicinal products must comply with their approved specifications and subject to compliance with GMP, can normally be released to market by performing a complete set of tests on active substances and/or finished products as defined in the relevant marketing authorization or clinical trial authorization. In specific circumstances, where authorised, based on product knowledge and process understanding, information collected during the manufacturing process can be used instead of end-product testing for batch release. Any separate activities required for this form of batch release should be integrated into the Pharmaceutical Quality System (PQS).

2. Scope

2.1 This document is intended to outline the requirements for application of Real Time Release Testing (RTRT) and parametric release, where the control of critical parameters and relevant material attributes are authorized as an alternative to routine end-product testing of active substances and/or finished products. A specific aim of this guideline is to incorporate the application of RTRT to any stage in the manufacturing process and to any type of finished products or active substances, including their intermediates

3. Real time release testing (RTRT)

3.1 Under RTRT, a combination of in-process monitoring and controls may provide, when authorized, substitute for end-product testing as part of the batch release decision. Interaction with all relevant regulatory authorities prior and during the assessment process preceding regulatory approval is required. The level of interaction will depend on the level of complexity of the RTRT control procedure applied on site.

3.2 When designing the RTRT strategy, the following minimum criteria are expected to be established and met:

i. Real time measurement and control of relevant in-process material attributes and process parameters should be accurate predictors of the corresponding finished product attributes.

ii. The valid combination of relevant assessed material attributes and process controls to replace finished product attributes should be established with scientific evidence based on material, product and process knowledge.

iii. The combined process measurements (process parameters and material attributes) and any other test data generated during the manufacturing process should provide a robust foundation for RTRT and the batch release decision.

3.3 A RTRT strategy should be integrated and controlled through the PQS. This should include or reference information at least of the following:

- quality risk management, including a full process related risk assessment, in accordance with the principles described in EudraLex, Volume 4, Part I Chapter 1 and Part II Chapter 2, - change control program,
- control strategy,
- specific personnel training program,
- qualification and validation policy,
- deviation/CAPA system,
- contingency procedure in case of a process sensor/equipment failure,
- periodic review/assessment program to measure the effectiveness of the RTRT plan for continued assurance of product quality.

3.4 In accordance with the principles described in EudraLex, Volume 4, Part I Chapter 1, Part II Chapter 13 and Annex 15, the change control program is an important part of the real time release testing approach. Any change that could potentially impact product manufacturing and testing, or the validated status of facilities, systems, equipment, analytical methods or processes, should be assessed for risk to product quality and impact on reproducibility of the manufacturing process. Any change should be justified by the sound application of quality risk management principles, and fully documented. After change implementation, an evaluation should be undertaken to demonstrate that there are no unintended or deleterious impact on product quality.

3.5 A control strategy should be designed not only to monitor the process, but also to maintain a state of control and ensure that a product of the required quality will be consistently produced. The control strategy should describe and justify the selected in-process controls, material attributes and process parameters which require to be routinely monitored and should be based on product, formulation and process understanding. The control strategy is dynamic and may change throughout the lifecycle of the product requiring the use of a quality risk management approach and of knowledge management. The control strategy should also describe the sampling plan and acceptance/rejection criteria.

3.6 Personnel should be given specific training on RTRT technologies, principles and procedures. Key personnel should demonstrate adequate experience, product and process knowledge and understanding. Successful implementation of RTRT requires input from a cross-functional/multi disciplinary team with relevant experience on specific topics, such as engineering, analytics, chemometric modelling or statistics.

3.7 Important parts of the RTRT strategy are validation and qualification policy, with particular reference to advanced analytical methods. Particular attention should be focused on the qualification, validation and management of in-line and on-line analytical methods, where the sampling probe is placed within the manufacturing equipment.

3.8 Any deviation or process failure should be thoroughly investigated and any adverse trending indicating a change in the state of control should be followed up appropriately.

3.9 Continuous learning through data collection and analysis over the life cycle of a product is important and should be part of the PQS. With advances in

technology, certain data trends, intrinsic to a currently acceptable process, may be observed. Manufacturers should scientifically evaluate the data, in consultation if appropriate, with the regulatory authorities, to determine how or if such trends indicate opportunities to improve quality and/or consistency.

3.10 When RTRT has been approved, this approach should be routinely used for batch release. In the event that the results from RTRT fail or are trending toward failure, a RTRT approach may not be substituted by end-product testing. Any failure should be thoroughly investigated and considered in the batch release decision depending on the results of these investigations, and must comply with the content of the marketing authorisation and GMP requirements. Trends should be followed up appropriately.

3.11 Attributes (e.g. uniformity of content) that are indirectly controlled by approved RTRT should still appear in the Certificate of Analysis for batches. The approved method for end-product testing should be mentioned and the results given as "Complies if tested" with a footnote: "Controlled by approved Real Time Release Testing".

4. Parametric release and sterilization

4.1 This section provides guidance on parametric release which is defined as the release of a batch of terminally sterilised product based on a review of critical process control parameters rather than requiring an end-product testing for sterility.

4.2 An end-product test for sterility is limited in its ability to detect contamination as it utilises only a small number of samples in relation to the overall batch size, and secondly, culture media may only stimulate growth of some, but not all, microorganisms. Therefore, an end-product testing for sterility only provides an opportunity to detect major failures in the sterility assurance system (i.e. a failure that results in contamination of a large number of product units and/or that result in contamination by the specific microorganisms whose growth is supported by the prescribed media). In contrast, data derived from in-process controls (e.g. pre-sterilization product bioburden or environmental monitoring) and by monitoring relevant sterilization parameters can provide more accurate and relevant information to support sterility assurance of the product.

4.3 Parametric release can only be applied to products sterilised in their final container using either moist heat, dry heat or ionising radiation (dosimetric release), according to European Pharmacopoeial requirements.

4.4 To utilise this approach, the manufacturer should have a history of acceptable GMP compliance and a robust sterility assurance program in place to demonstrate consistent process control and process understanding.

4.5 The sterility assurance program should be documented and include, at least, the identification and monitoring of the critical process parameters, sterilizer cycle development and validation, container/packaging integrity validation, bioburden control, environmental monitoring program, product segregation plan, equipment, services and facility design and qualification program, maintenance

and calibration program, change control program, personnel training, and incorporate a quality risk management approach.

4.6 Risk management is an essential requirement for parametric release and should focus on mitigating the factors which increase the risk of failure to achieve and maintain sterility in each unit of every batch. If a new product or process is being considered for parametric release, then a risk assessment should be conducted during process development including an evaluation of production data from existing products if applicable. If an existing product or process is being considered, the risk assessment should include an evaluation of any historical data generated.

4.7 Personnel involved in the parametric release process should have experience in the following areas: microbiology, sterility assurance, engineering, production and sterilization. The qualifications, experience, competency and training of all personnel involved in parametric release should be documented.

4.8 Any proposed change which may impact on sterility assurance should be recorded in the change control system and reviewed by appropriate personnel who are qualified and experienced in sterility assurance.

4.9 A pre-sterilization bio-burden monitoring program for the product and components should be developed to support parametric release. The bioburden should be performed for each batch. The sampling locations of filled units before sterilization should be based on a worst-case scenario and be representative of the batch. Any organisms found during bioburden testing should be identified to confirm that they are not spore forming which may be more resistant to the sterilizing process.

4.10 Product bio-burden should be minimized by appropriate design of the manufacturing environment and the process by:

- good equipment and facility design to allow effective cleaning, disinfection and sanitisation;
- availability of detailed and effective procedures for cleaning, disinfection and sanitisation;
- use of microbial retentive filters where possible;
- availability of operating practices and procedures which promote personnel hygiene and enforce appropriate garment control;
- appropriate microbiological specifications for raw materials, intermediates and process aids (e.g. gases)

4.11 For aqueous or otherwise microbiologically unstable products, the time lag between dissolving the starting materials, product fluid filtration, and sterilization should be defined in order to minimise the development of bioburden and an increase in endotoxins (if applicable).

Sterilization Process

4.12 Qualification and validation are critical activities to assure that sterilization equipment can consistently meet cycle operational parameters and that the monitoring devices provide verification of the sterilization process

4.13 Periodic requalification of equipment and revalidation of processes should be planned and justified in accordance with the requirements of Annexes 1 and 15.

4.14 Appropriate measurement of critical process parameters during sterilization is a critical requirement in a parametric release program. The standards used for process measuring devices should be specified and the calibration should be traceable to national or international standards.

4.15 Critical process parameters should be established, defined and undergo periodic re-evaluation. The operating ranges should be developed based on sterilization process, process capability, calibration tolerance limits and parameter criticality.

4.16 Routine monitoring of the sterilizer should demonstrate that the validated conditions necessary to achieve the specified process is achieved in each cycle. Critical processes should be specifically monitored during the sterilization phase.

4.17 The sterilization record should include all the critical process parameters. 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.

4.18 Once parametric release has been approved by the regulatory authorities, decisions for release or rejection of a batch should be based on the approved specifications and the review of critical process control data. Routine checks of the sterilizer, changes, deviations, unplanned and routine planned maintenance activities should be recorded, assessed and approved before releasing the products to the market. Non-compliance with the specification for parametric release cannot be overruled by a finished product passing the test for sterility.

5. Glossary

Control strategy

A planned set of controls, derived from current product and process understanding that ensures 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.

Critical Process Parameters:

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality [ICH Q8 (R2)].

Critical Quality Attributes

A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. [ICH Q8 (R2)]

Parametric release

One form of RTRT. Parametric release for terminally sterilised product is based on the review of documentation on process monitoring (e.g. temperature, pressure, time for terminal sterilization) rather than the testing of a sample for a specific attribute

(ICH Q8 Q&A). (Together with compliance with specific GMP requirements related to parametric release this provides the desired assurance of the quality of the product.) (EMA guideline on Real-Time Release Testing)

Real time release testing

The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls. (ICH Q8)

State of Control

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

Annex 19
Reference and Retention Sample

1. Scope

1.1 This Annex to the Guide to Good Manufacturing Practice for Medicinal Products ("the GMP Guide") gives guidance on the taking and holding of reference samples of starting materials, packaging materials or finished products and retention samples of finished products.

1.2 Specific requirements for investigational medicinal products are given in Annex 13 to the Guide.

1.3 This annex also includes guidance on the taking of retention samples for parallel imported/ distributed medicinal products.

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 (for veterinary medicinal products other than immunologicals, see also Annex 4, paragraphs 8 & 9).

3.2 Unless a longer period is required under the law of the Member State of manufacture, 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 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.

10.3 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.

Annex 20
Quality Risk Management

Foreword and Scope of Application

The new GMP Annex 20 corresponds to ICH Q9 guideline on Quality Risk Management. It provides guidance on a systematic approach to quality risk management facilitating compliance with GMP and other quality requirements. It includes principles to be used and options for processes, methods and tools which may be used when applying a formal quality risk management approach.

To ensure coherence, GMP Part I, Chapter 1 on Quality Management, has been revised to include aspects of quality risk management within the quality system framework. A similar revision is planned for Part II of the Guide. Other sections of the GMP guide may be adjusted to include aspects of quality risk management in future broader revisions of those sections.

With the revision of the chapters on quality management in GMP Parts I and II quality risk management becomes an integral part of a manufacturer’s quality system. Annex 20 itself is not intended, however, to create any new regulatory expectations; it provides an inventory of internationally acknowledged risk management methods and tools together with a list of potential applications at the discretion of manufacturers.

It is understood that the ICH Q9 guideline was primarily developed for quality risk management of medicinal products for human use. With the implementation in Annex 20 benefits of the guideline, such as processes, methods and tools for quality risk management are also made available to the veterinary sector.

While the GMP guide is primarily addressed to manufacturers, the ICH Q9 guideline, has relevance for other quality guidelines and includes specific sections for regulatory agencies. However, for reasons of coherence and completeness, the ICH Q9 guideline has been transferred completely into GMP Annex 20.

Further consideration of regulatory aspects, such as with the revision of the "Compilation of Community Procedures on Inspections and Exchange of Information" and in some quality guidelines, as published by the EMEA, will follow in a step-by-step approach.

1. 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 pharmaceuticals, 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 drug (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, 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 labeling materials in drug (medicinal) products, biological and biotechnological products).

3. Principles of Quality Risk Management

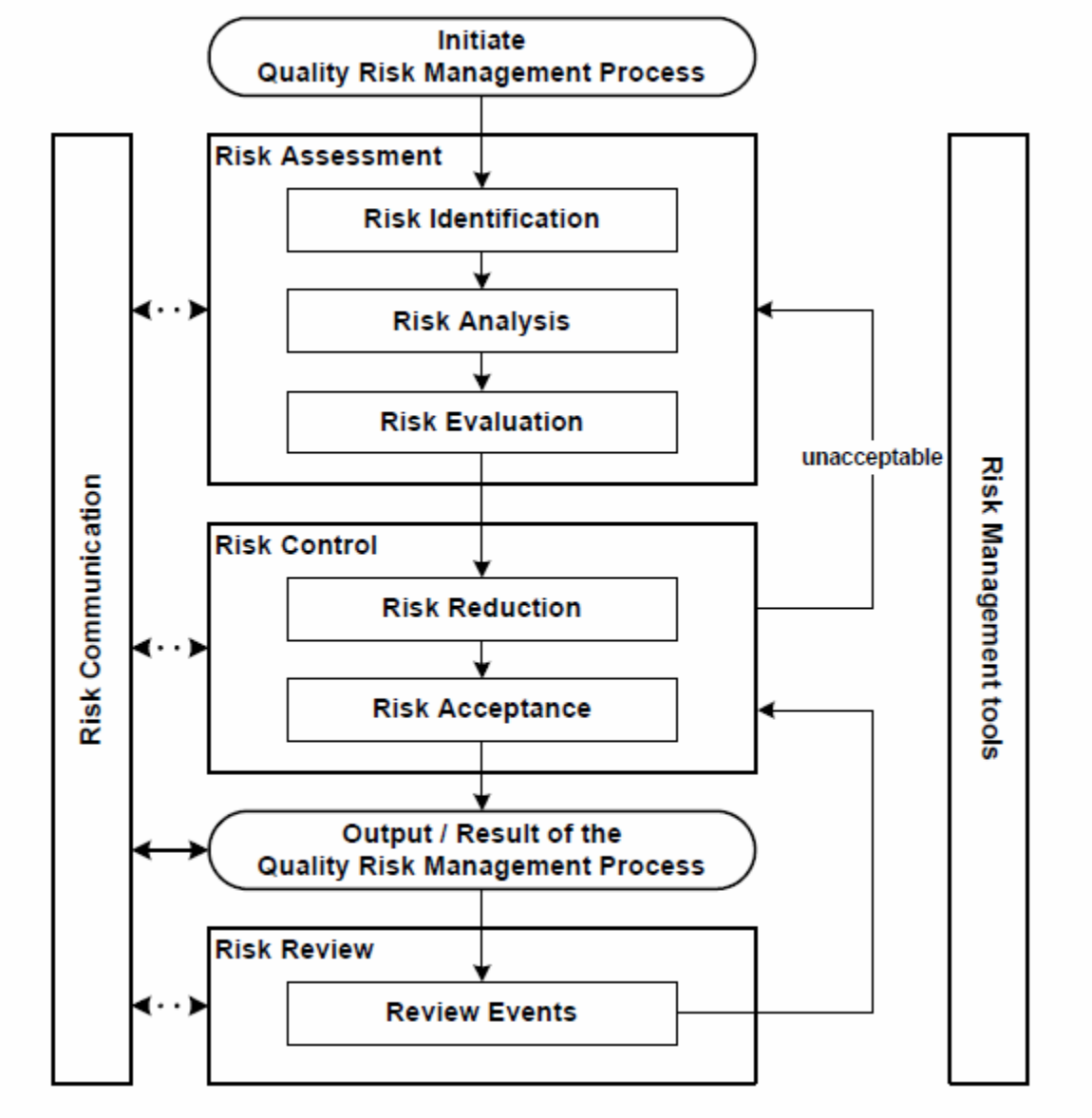
Two primary principles of quality risk management are:

- 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 drug (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
- assure 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 analyzed 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 existence, 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 guidance.

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

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 industry and 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 labeling

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 fulfills 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 authority, 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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IEC 61882 - Hazard Operability Analysis (HAZOP)

ISO 14971:2000 - Application of Risk Management to Medical Devices

ISO 7870:1993 - Control Charts

ISO 7871:1997 - Cumulative Sum Charts

ISO 7966:1993 - Acceptance Control Charts

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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 one 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 diagram 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(s)
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 Areas of Use(s)

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.

I.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 subsystem) 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 Areas of Use(s)

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 analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of 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 Areas of Use(s)

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 Areas of Use(s)

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 Areas of Use(s)

PHA might be useful when analyzing 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 Areas of Use(s)

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)

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 that allow 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 final 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

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 facility / 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., multiversus single-purpose, batch versus continuous production)
To determine acceptable (specified) cleaning validation limits

Calibration/preventive maintenance
To set appropriate calibration and maintenance schedules

Computer 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

Annex 21: Importation of medicinal products

1. Scope

This Annex summarizes the GMP requirements applicable to a Manufacturing Import Authorisation (MIA) holder, when importing medicinal products (human, investigational and veterinary) from outside the EU/EEA. The guidance in the main chapters and other annexes of the Guide to Good Manufacturing Practice for Medicinal Products ("the EU GMP Guide") also apply, as appropriate, for other GMP activities carried out and should be consulted for supplementary guidance. Medicinal products that enter the EU/EEA with the intention of export only and that are not processed in any form nor released for placing on the EU/EEA market, are not covered by this Annex.

2. Principles

2.1 For the purpose of this annex, the term importation refers to the action of physically bringing a medicinal product, from outside the territory of EEA/EU; fiscal transactions are not part of this annex. Qualified Person (QP) certification or confirmation, as appropriate, of a batch of a medicinal product takes place only after physical importation and custom clearance into the customs territory of an EU/EEA State. Imported bulk products and intermediate products may undergo further manufacturing operations in accordance with the marketing authorisation or clinical trial authorisation prior to QP certification or confirmation, as appropriate. The sites which are considered to have specific importation responsibilities in relation to a medicinal product, a bulk or an intermediate product, are:

a) Site of Physical Importation.

b) Site of QP certification of imported medicinal products or QP confirmation for bulk or intermediate products undergoing further processing, as appropriate. The above importation responsibilities must be carried out by entities appropriately authorized under a MIA.

2.2 All stages of manufacture of imported medicinal products that are carried out in third countries should be conducted in accordance with the EU GMP Guide or equivalent standards and in conformance with the Marketing Authorisation (MA), the clinical trial authorisation (CTA) and the relevant quality agreement, as applicable.

2.3 For products authorized in the EU/EEA, the overall responsibility for placing the medicinal products on the market lies with the marketing authorisation holder (MAH).

2.4 The Qualified Person certifying the batch must ensure that all the medicinal products for human or veterinary use or investigational medicinal products that are imported into the Union from a third country were manufactured in accordance with the EU GMP Guide or recognised equivalent standards, and for products with a marketing authorisation, tested upon importation in the Union , unless there are appropriate arrangements in place between the Union and the third country (e.g. Mutual Recognition Agreement (MRA) or Agreement on conformity assessment and acceptance of industrial products, ACAA). See also Annex 16 of the EU GMP

Guide and Annex 13, the detailed guidelines on GMP for Investigational Medicinal Products (IMPs) for further guidance.

2.5 Testing in an EU/EEA state should cover all the tests needed to demonstrate that the medicinal product meets the specifications that are set out in the marketing authorisation.

2.6 Written agreements should be in place between the site(s) performing manufacturing, importation activities and the MAH or sponsor, as appropriate, in accordance with Chapter 7 of the EU GMP Guide.

3. Pharmaceutical Quality System

3.1 The site(s) conducting importation activities should have an appropriately detailed Pharmaceutical Quality System in accordance with Chapter 1 of the EU GMP Guide and reflecting the scope of the activities carried out.

3.2 Product Quality Reviews should be performed by the site responsible for QP certification for the products imported, including products imported for further processing before export with the exception of investigational medicinal products.

- Written agreements should be in place to define the respective responsibilities of the MAH, the importer(s), the site responsible for QP certification and the third country manufacturers, as appropriate, in relation to compiling of the Product Quality Reviews as outlined in Chapter 1 of the EU GMP Guide.
- In addition to the Product Quality Review (PQR) requirements described in Chapter 1 of the EU GMP Guide, where sampling of the imported product is conducted in a third country in accordance with Annex 16 of the EU GMP Guide, the PQR should include an assessment of the basis for continued reliance on this sampling practice. PQRs should also include a review of deviations relating to transportation up to the point of batch certification. Specific requirements for sampling and transportation of imported products are detailed further in Annex 16 of the EU GMP Guide.
- As part of this review, the analytical results from importation testing should be compared with those in the Certificate of Analysis generated by the third country manufacturer. Any discrepancies or out of trends (OOT) should be documented and investigated.

4. Premises and equipment

4.1 The site(s) involved in importation activities should have adequate premises and equipment to ensure the respective activities are performed in accordance with EU GMP Guide.

4.2 Imported medicinal products should be stored under quarantine after receipt, until their release for further processing or following QP certification or confirmation as appropriate, in accordance with Annex 16 of the EU GMP Guide. Segregated areas should exist for quarantined products. Any system replacing the physical quarantine should ensure an equivalent level of security.

5. Documentation

5.1 Full batch documentation must be available to the MIA holder responsible for QP certification or confirmation of the batch, as appropriate, at the time of certification or confirmation of the batch. Other MIA holders involved in the importation process should have access to batch documentation as necessary in accordance with the activities for which the site is responsible, and as reflected in written agreements between the parties involved in the importation process.

5.1.1 The site responsible for QP certification or confirmation, as appropriate, should have access to those documents that would support batch certification as defined in Annex 16 of the EU GMP Guide. The frequency at which full batch documentation is reviewed at the site responsible for QP certification or confirmation, as appropriate, of the product should be justified on a risk assessment basis and defined in the Pharmaceutical Quality System. Documentary evidence should be available to demonstrate that the QP has certified or confirmed the batch in accordance with the MA or clinical trial authorisation and any other regulatory restrictions that may apply (e.g. where an EU GMP certificate restricts activities to specific manufacturing units/buildings at the third country manufacturing site).

5.1.2 The documentation on the site of physical importation should include, at a minimum, the details of transportation and receipt of the product (see also Annex 16 of the EU GMP Guide).

5.1.3 Relevant ordering and delivery documentation should be available for inspection at the site responsible for QP certification or confirmation, as appropriate, and clearly indicate:

- The site from where the product has been dispatched (the origin of the product).
- The site of physical importation.
- Shipping details (including transportation route and temperature monitoring records) and customs documentation, such as the packing list, freight documentation or customs import declaration, as applicable

5.2 Documentation must be retained in accordance with the requirements of Chapter 4 of the EU GMP Guide. The site responsible for QP certification should ensure that the third country manufacturing site has a record retention policy equivalent to EU requirements.

5.3 Batch documentation, including batch certificates, supplied by the third country manufacturing site should be in a format understood by the importer. It may be necessary to provide documents in more than one language to facilitate understanding.

5.4 There should be documentary evidence that the site performing QP certification has qualified the third country manufacturer and regularly monitors its performance by periodic on-site audits, either by the site performing QP certification or by a third party on its behalf in accordance with Annex 16 of the EU GMP Guide, to ensure that the imported products are manufactured in accordance with EU GMP rules or equivalent requirements and the MA or clinical trial authorisation.

5.5 Where batches have been subdivided and the individual quantities imported separately, documentation confirming reconciliation of the quantities should be made available at the site responsible for QP certification. Any discrepancy should be investigated under the responsibility of the certifying QP.

6. Operations

6.1 The site responsible for QP certification should ensure that an ongoing stability program is in place, as required in Chapter 6 of the EU GMP Guide. The ongoing stability program may be carried out at a third country site as an outsourced activity provided that the QP has all the necessary information to assure ongoing product quality. Details of the ongoing stability program, such as protocols, results and reports should be available for inspection at the site responsible for QP certification.

6.2 The QP certifying the batch is responsible for ensuring that, where required, the safety features have been affixed to the packaging.

6.3 The certifying QP is also responsible for ensuring that reference and retention samples have been taken in accordance with the requirements in Annex 19 of the EU GMP Guide and applicable detailed guidelines for GMP for IMPs.

7. Complaints, Quality Defects and Product Recalls

7.1 Adequate provisions should be in place between the site(s) performing importation activities, the third country manufacturer and the MAH or sponsor for handling complaints, quality defects and product recalls as required in Chapter 8 of the EU GMP Guide. These should be defined in contractual arrangements.