PART 1

BASIC REQUIREMENTS FOR HUMAN MEDICINAL PRODUCTS

CHAPTER 1

QUALITY MANAGEMENT

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

The basic concepts of Quality Assurance, Good Manufacturing Practice, Quality Control and Quality Risk Management are inter-related. They are described here in order to emphasise their relationships and their fundamental importance to the production and control of medicinal products.

QUALITY ASSURANCE

1.1 Quality Assurance is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It 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 Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this Guide.

The system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that:

i. medicinal products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practice ;

ii. production and control operations are clearly specified and Good Manufacturing Practice adopted;

iii. managerial responsibilities are clearly specified;

iv. arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;

v. all necessary controls on intermediate products, and any other in-process controls and validations are carried out;

vi. the finished product is correctly processed and checked, according to the defined procedures;

vii. medicinal products are not sold or supplied before the Responsible person has certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorisation and any other regulations relevant to the production, control and release of medicinal products;

viii. satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life;

ix. there is a procedure for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the quality assurance system.

GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS (GMP)

1.2 Good Manufacturing Practice is that part of Quality Assurance which ensures that Medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation or product specification.

Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that:

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

ii. critical steps of manufacturing processes and significant changes to the process are validated;

iii. all necessary facilities for GMP are provided including:

a. appropriately qualified and trained personnel;

b. adequate premises and space;

c. suitable equipment and services;

d. correct materials, containers and labels;

e. approved procedures and instructions;

f. suitable storage and transport;

iv. instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities

provided;

v. operators are trained to carry out procedures correctly;

vi. records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated;

vii. records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

viii. the distribution (wholesaling) of the products minimises any risk to their quality;

ix. a system is available to recall any batch of product, from sale or supply;

x. complaints about marketed products are examined, the causes of quality defects investigated and appropriate measures taken in respect of the defective products and to prevent re-occurrence.

QUALITY CONTROL

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

The basic requirements of Quality Control are that:

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

ii. samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by personnel and by methods approved by Quality Control;

iii. test methods are validated;

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

v. the finished products contain active ingredients complying with the qualitative and quantitative composition of the marketing authorisation, are of the 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 the Responsible person that it is in accordance with the requirements of the relevant authorisations;

viii. sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

PRODUCT QUALITY REVIEW

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

i. A review of starting materials including packaging materials used in the product, especially those from new sources.

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

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

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

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

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

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

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

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

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

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

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

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

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

QUALITY RISK MANAGEMENT

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

1.6 The quality risk management system should ensure that:

- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;
- the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

Examples of the processes and applications of quality risk management can be found inter alia in Annex 16.

CHAPTER 2

PERSONNEL

PRINCIPLE

The establishment and maintenance of a satisfactory system of quality assurance and 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. 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. 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.

KEY PERSONNEL

2.3. Key Personnel includes the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the release of products the R esponsible person 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 2.5., 2.6. and 2.7.

2.4. The duties of a Responsible Person can be summarized as follows:

a) The Responsible Person must ensure that each batch has been produced and tested/checked in accordance with the legal requirements and the marketing authorisation;

b) The Responsible Person must ensure that each imported batch has been tested in the importing country;

c) The Responsible Person must certify in a register or document, as operations are carried out and before any release, that each production batch satisfies the required provisions.

The persons responsible for these duties must meet the specified qualification requirements; they should be continuously at the disposal of the Manufacturing Authorisation Holder to carry out their responsibilities. Their responsibilities may be delegated only to other qualified personnel.

2.5. The head of the Production Department generally has the following responsibilities:

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

ii. to approve the instructions relating to production operations and to ensure their strict implementation;

iii. to ensure that the production records are evaluated and signed by a responsible person before they are sent to the Quality Control Department;

iv. to check the maintenance of his department, premises and equipment;

v. to ensure that the appropriate validations are done;

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

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

i. to approve or reject, as he sees fit, starting materials, packaging materials, and intermediate, bulk and finished products;

ii. to evaluate batch records;

iii. to ensure that all necessary testing is carried out;

iv. to approve specifications, sampling instructions, test methods and other Quality Control procedures;

v. to approve and monitor any contract analysts;

vi. to check the maintenance of his department, premises and equipment;

vii. to ensure that the appropriate validations are done;

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

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

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

- the authorisation of written procedures and other documents, including amendments;
- the monitoring and control of the manufacturing environment;
- plant hygiene;
- process validation;
- training;
- the approval and monitoring of suppliers of materials;

- the approval and monitoring of contract manufacturers;
- the designation and monitoring of storage conditions for materials and products;
- the retention of records;
- the monitoring of compliance with the requirements of GMP;
- the inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality.

TRAINING

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

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

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

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

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

PERSONNEL HYGIENE

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

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

2.15. 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.

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

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

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

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

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

CHAPTER 3

PREMISES AND EQUIPMENT

PRINCIPLE

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

PREMISES

General

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

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

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

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

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

Production Area

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

3.7. Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

3.8. The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimise the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimise the risk of omission or wrong application of any of the manufacturing or control steps.

3.9. Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.

3.10. 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 that use.

3.14. In cases where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross-contamination and facilitate cleaning.

3.15. Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

3.16. Productions areas should be well lit, particularly where visual on-line controls are carried out.

3.17. In-process controls may be carried out within the production area provided they do not carry any risk for the production.

Storage Areas

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

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

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

3.21. Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to responsible 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 products and special attention should be paid to the safe and secure storage of these materials.

Quality Control Areas

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

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

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

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

Ancillary Areas

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

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

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

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

EQUIPMENT

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

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

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

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

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

3.39. Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

3.40. Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.

3.41. Measuring, weighing, recording and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

3.42. Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

3.43. Distilled, deionized and, where appropriate, other water pipes should be sanitised according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

3.44. Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

CHAPTER 4

DOCUMENTATION

PRINCIPLE

Good documentation constitutes an essential part of the quality assurance system and is key to operating in compliance with GMP requirements. The various types of documents and media used 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 utilised 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.

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

GENERATION AND CONTROL OF DOCUMENTATION

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

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

4.3 Documents containing instructions should be approved, signed and dated by appropriate and responsible 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.

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

4.5 Documents within the Quality Management System should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.

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

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

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

SPECIFICATIONS

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

Specifications for starting and packaging materials

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

a) A description of the materials, including:
   - The designated name and the internal code reference;
   - The reference, if any, to a pharmacopoeial monograph;
   - The approved suppliers and, if reasonable, the original producer of the material;
   - A specimen of printed materials;

b) Directions for sampling and testing;

c) Qualitative and quantitative requirements with acceptance limits;

d) Storage conditions and precautions;

e) The maximum period of storage before re-examination.

Specifications for intermediate and bulk products

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

Specifications for finished products

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

a) The designated name of the product and the code reference where applicable;

b) The formula;

c) A description of the pharmaceutical form and package details;

d) Directions for sampling and testing;

e) The qualitative and quantitative requirements, with the acceptance limits;

f) The storage conditions and any special handling precautions, where applicable;

g) The shelf-life.

MANUFACTURING FORMULA AND PROCESSING INSTRUCTIONS

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

4.17 The Manufacturing Formula should include:

a) The name of the product, with a product reference code relating to its specification;

b) A description of the pharmaceutical form, strength of the product and batch size;

c) A list of all starting materials to be used, with the amount of each, described; mention should be made of any substance that may disappear in the course of processing;

d) A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

4.18 The Processing Instructions should include:

a) A statement of the processing location and the principal equipment to be used;

b) The methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilising);

c) Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use;

d) Detailed stepwise processing instructions [e.g. checks on materials, pre-treatments, sequence for adding materials, critical process parameters (time, temp etc)];

e) The instructions for any in-process controls with their limits;

f) Where necessary, the requirements for bulk storage of the products; including the container, labeling and special storage conditions where applicable;

g) Any special precautions to be observed.

Packaging Instructions

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

a) Name of the product; including the batch number of bulk and finished product;

b) Description of its pharmaceutical form, and strength where applicable;

c) The pack size expressed in terms of the number, weight or volume of the product in the final container;

d) A complete list of all the packaging materials required, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;

e) Where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;

f) Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations (line clearance), and that equipment is clean and suitable for use;

g) Special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;

h) A description of the packaging operation, including any significant subsidiary operations, and equipment to be used;

i) Details of in-process controls with instructions for sampling and acceptance limits.

Batch Processing Record

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

a) The name and batch number of the product;

b) Dates and times of commencement, of significant intermediate stages and of completion of production;

c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;

d) The batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);

e) Any relevant processing operation or event and major equipment used;

f) A record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;

g) The product yield obtained at different and pertinent stages of manufacture;

h) Notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula and Processing Instructions;

i) Approval by the person responsible for the processing operations.

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

Batch Packaging Record

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

The batch packaging record should contain the following information:

a) The name and batch number of the product;

b) The date(s) and times of the packaging operations;

c) Identification (initials) of the operator(s) who performed each significant step of the process and, where appropriate, the name of any person who checked these operations;

d) Records of checks for identity and conformity with the packaging instructions, including the results of in-process controls;

e) Details of the packaging operations carried out, including references to equipment and the packaging lines used;

f) Whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;

g) Notes on any special problems or unusual events including details, with signed authorisation for any deviation from the Packaging Instructions;

h) The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation. Where there are robust electronic controls in place during packaging there may be justification for not including this information;

i) Approval by the person responsible for the packaging operations.

PROCEDURES AND RECORDS

Receipt

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

4.23 The records of the receipts should include:

a) The name of the material on the delivery note and the containers;

b) The "in-house" name and/or code of material (if different from a);

c) Date of receipt;

d) Supplier's name and manufacturer's name;

e) Manufacturer's batch or reference number;

f) Total quantity and number of containers received;

g) The batch number assigned after receipt;

h) Any relevant comment.

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

Sampling

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

Testing

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

Other

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

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

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

- Validation and qualification of processes, equipment and systems;

- Equipment assembly and calibration;

- Technology transfer;

- Maintenance, cleaning and sanitation;

- Personnel matters including signature lists, training in GMP and technical matters, clothing and hygiene and verification of the effectiveness of training;

- Environmental monitoring;

- Pest control;
- Complaints;
- Recalls;
- Returns;
- Change control;
- Investigations into deviations and non-conformances;
- Internal quality/GMP compliance audits;
- Summaries of records where appropriate (e.g. product quality review);
- Supplier audits.

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

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

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

CHAPTER 5

PRODUCTION

PRINCIPLE

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

GENERAL

5.1. Production should be performed and supervised by competent people.

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

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

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

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

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

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

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

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

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

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

5.12. At all times during processing, all materials, bulk containers, major items of equipment and where appropriate rooms used should be labelled or otherwise

identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production.

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

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

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

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

5.17. Normally, the production of non-medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.

PREVENTION OF CROSS-CONTAMINATION IN PRODUCTION

5.18. Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Amongst the most hazardous contaminants are highly sensitising materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time.

5.19. Cross-contamination should be avoided by appropriate technical or organisational measures, for example:

a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;

b) providing appropriate air-locks and air extraction;

c) minimising the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;

d) keeping protective clothing inside areas where products with special risk of cross-contamination are processed;

e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;

f) using "closed systems" of production;

g) testing for residues and use of cleaning status labels on equipment.

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

VALIDATION

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

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

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

5.24. Processes and procedures should undergo periodic critical revalidation to ensure that they remain capable of achieving the intended results.

STARTING MATERIALS

5.25. The purchase of starting materials is an important operation which should involve staff who have a particular and thorough knowledge of the suppliers.

5.26. Starting materials should only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements, as well as complaints and rejection procedures are discussed with the manufacturer and the supplier.

5.27. For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.

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

5.29. Starting materials in the storage area should be appropriately labelled (see Chapter 5, Item 13). Labels should bear at least the following information:

- the designated name of the product and the internal code reference where applicable;
- a batch number given at receipt;
- where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);
- where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully computerised storage systems are used, all the above information

should not necessarily be in a legible form on the label.

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

5.31. Only starting materials which have been released by the Quality Control Department and which are within their shelf-life should be used.

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

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

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

PROCESSING OPERATIONS - INTERMEDIATE AND BULK PRODUCTS

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

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

5.37. Critical processes should be validated (see "VALIDATION" in this Chapter).

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

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

PACKAGING MATERIALS

5.40. The purchase, handling and control of primary and printed packaging materials should be accorded attention similar to that given to starting materials.

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

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

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

PACKAGING OPERATIONS

5.44. When setting up a programme for the packaging operations, particular attention

should be given to minimising the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

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

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

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

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

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

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

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

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

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

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

a) general appearance of the packages;

b) whether the packages are complete;

c) whether the correct products and packaging materials are used;

d) whether any over-printing is correct;

e) correct functioning of line monitors.

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

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

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

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

FINISHED PRODUCTS

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

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

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

REJECTED, RECOVERED AND RETURNED MATERIALS

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

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

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

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

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

CHAPTER 6

QUALITY CONTROL

PRINCIPLE

Quality Control is concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality Control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control (see also Chapter 1).

GENERAL

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

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

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

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

GOOD QUALITY CONTROL LABORATORY PRACTICE

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

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

particular reasons, but this should be stated in the Quality Control records.

DOCUMENTATION

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

- specifications;
- sampling procedures;
- testing procedures and records (including analytical worksheets and/or laboratory notebooks);
- analytical reports and/or certificates;
- data from environmental monitoring, where required;
- validation records of test methods, where applicable;
- procedures for and records of the calibration of instruments and maintenance of equipment.

6.8. Any Quality Control documentation relating to a batch record should be retained for one year after the expiry date of the batch and at least 5 years as specified in the Regulation on the Manufacturing Sites for Human Medicinal Products.

6.9. For some kinds of data (e.g. analytical tests results, yields, environmental controls, ...) it is recommended that records in a manner permitting trend evaluation be kept.

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

SAMPLING

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

- the method of sampling;
- the equipment to be used;
- the amount of the sample to be taken;
- instructions for any required sub-division of the sample;
- the type and condition of the sample container to be used;
- the identification of containers sampled;
- any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
- the storage conditions;
- instructions for the cleaning and storage of sampling equipment.

6.12. Reference samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a

process).

6.13. Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn.

6.14. Reference samples from each batch of finished products should be retained till one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. Samples of starting materials (other than solvents, gases and water) should be retained for at least two years after the release of the product if their stability allows. This period may be shortened if their stability, as mentioned in the relevant specification, is shorter. Reference samples of materials and products should be of a size sufficient to permit at least two full re-examination or a size approved by the Agency.

TESTING

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

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

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

a) name of the material or product and, where applicable, dosage form;

b) batch number and, where appropriate, the manufacturer and/or supplier;

c) references to the relevant specifications and testing procedures;

d) test results, including observations and calculations, and reference to any certificates of analysis;

e) dates of testing;

f) initials of the persons who performed the testing;

g) initials of the persons who verified the testing and the calculations, where appropriate;

h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

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

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

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

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

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

ON-GOING STABILITY PROGRAMME

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

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

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

6.26. The on-going stability programme should be described in a written protocol following the general rules of Chapter 4 and results formalised as a report. The equipment used for the on-going stability programme (stability chambers among others) should be qualified and maintained following the general rules of Chapter 3 and annex 13.

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

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

• other applicable parameters specific to the medicinal product.

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

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

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

6.31. Results of on-going stability studies should be made available to key personnel and, in particular, to the Responsible person. 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 Agency.

6.32. Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to the Agency. 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 Agency.

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

CHAPTER 7

CONTRACT MANUFACTURE AND ANALYSIS

PRINCIPLE

Contract manufacture and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product or work of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party. The contract must clearly state the way in which the responsible person releasing each batch of product for sale exercises his full responsibility.

Note: This Chapter deals with the responsibilities of manufacturers towards the Component Authorities of the Participating Authorities with respect to the granting of marketing and manufacturing authorisations. It is not intended in any way to affect the respective liability of contract acceptors and contract givers to consumers.

GENERAL

7.1. There should be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.

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

THE CONTRACT GIVER

7.3. The Contract Giver is responsible for assessing the competence of the Contract Acceptor to carry out successfully the work required and for ensuring by means of the contract that the principles and Guidelines of GMP as interpreted in this Guide are followed.

7.4. The Contract Giver should provide the Contract Acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorisation and any other legal requirements. 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.

7.5. The Contract Giver should ensure that all processed products and materials delivered to him by the Contract Acceptor comply with their specifications or that the products have been released by the Responsible person.

THE CONTRACT ACCEPTOR

7.6. The Contract Acceptor must have adequate premises and equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the Contract Giver. Contract manufacture may be undertaken only by a manufacturer who is the holder of a manufacturing authorisation.

7.7. The Contract Acceptor should ensure that all products or materials delivered to him are suitable for their intended purpose.

7.8. The Contract Acceptor should not pass to a third party any of the work entrusted to him under the contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original Contract Giver and Contract Acceptor.

7.9. The Contract Acceptor should refrain from any activity which may adversely affect the quality of the product manufactured and/or analysed for the Contract Giver.

THE CONTRACT

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

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

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

7.13. 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 must be accessible and specified in the defect/recall procedures of the Contract Giver.

7.14. The contract should permit the Contract Giver to visit the facilities of the Contract Acceptor.

7.15. In case of contract analysis, the Contract Acceptor should understand that he is subject to inspection by the Agency.

CHAPTER 8

COMPLAINTS AND PRODUCT RECALL

PRINCIPLE

All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures. In order to provide for all contingencies, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

COMPLAINTS

8.1. A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him. If this person is not the Responsible person, the latter should be made aware of any complaint, investigation or recall.

8.2. There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

8.3. Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control should normally be involved in the study of such problems.

8.4. If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches in order to determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch should be investigated.

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

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

8.7. Special attention should be given to establishing whether a complaint was caused because of counterfeiting.

8.8. The Agency should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, detection of counterfeiting or any other serious quality problems with a product.

RECALLS

8.9. A person should be designated as responsible for execution and co-ordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person

should normally be independent of the sales and marketing organisation. If this person is not the Responsible person, the latter should be made aware of any recall operation.

8.10. There should be established written procedures, regularly checked and updated when necessary, in order to organise any recall activity.

8.11. Recall operations should be capable of being initiated promptly and at any time.

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

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

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

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

8.16. The effectiveness of the arrangements for recalls should be evaluated regularly.

8.17. Requirements of the "Regulation on Recalls" is exactly applicable to recall procedures.

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.

PART 2

BASIC REQUIREMENTS FOR ACTIVE PHARMACEUTICAL INGREDIENTS

1. Introduction

As per the Regulation on Manufacturing Sites for Human Medicinal Products, active pharmaceutical ingredients may only be used if the manufacturing site is in compliance with GMP requirements. This chapter is dedicated to active pharmaceutical ingredients; other relevant chapters of the GMP guide are also applicable.

1.1 Objective

This document (Guide) is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

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

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

This Guide is not intended to define registration requirements or modify pharmacopoeial requirements and does not affect the ability of the Agency to establish specific registration requirements regarding APIs within the context of marketing/manufacturing authorisations. All commitments in registration documents must be met.

1.2 Scope

This Guide applies to the manufacture of APIs for medicinal products for human use. It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilisation and aseptic processing of sterile APIs are not covered, but should be performed in accordance with the principles and guidelines of GMP as laid down in national legislations and interpreted in the GMP Guide including its Annex 1.

This Guide excludes whole blood and plasma and the detailed requirements for the collection and testing of blood. However, it does include APIs that are produced using blood or plasma as raw materials.

Finally, the Guide does not apply to bulk-packaged human medicinal products. It applies to all other active starting materials subject to any derogations described in the annexes to the GMP Guide, in particular Annexes 2 to 5 where supplementary guidance for certain types of API may be found. The annexes will consequently undergo a review but in the meantime and only until this review is complete, manufacturers may choose to continue to use Part I of the basic requirements and the relevant annexes for products covered by those annexes, or may already apply Part II.

Section 19 contains guidance that only applies to the manufacture of APIs used in the production of investigational medicinal products.

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

The manufacturer should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which "API Starting Materials" are entered into the process. For other processes (e.g. fermentation, extraction, purification, etc), this rationale should be established on a case-by-case basis. Table 1 gives guidance on the point at which the API Starting Material is normally introduced into the process.

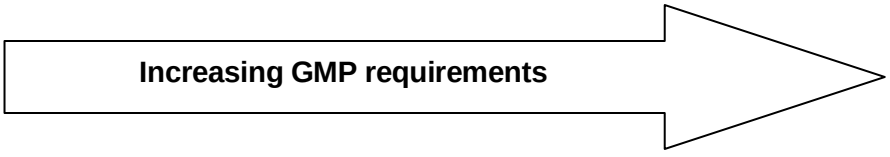
From this point on, appropriate Good Manufacturing Practices as defined in this Guide should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a manufacturer chooses to validate a process step does not necessarily define that step as critical.

The guidance in this document would normally be applied to the steps shown in gray in Table 1. It does not imply that all steps shown should be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification, and packaging. Physical processing of APIs, such as granulation, coating or physical manipulation of particle size (e.g. milling, micronizing), should be conducted at least to the standards of this Guide.

This GMP Guide does not apply to steps prior to the introduction of the defined "API Starting Material".

Table 1: Application of this Guide to API Manufacturing

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



2. QUALITY MANAGEMENT

2.1 Principles

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

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

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

2.13 There should be a quality unit(s) that is independent of production and that fulfils both quality assurance *(QA)* and quality control *(QC)* responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

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

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

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

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

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

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

2.2 Quality Risk Management

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

2.21 The quality risk management system should ensure that:

- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient through communication with the user of the active substance.

- the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

Examples of the processes and applications of quality risk management can be found, inter alia, in Annex 16.

2.3 Responsibilities of the Quality Unit(s)

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

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

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

1. Releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company;

2. Establishing a system to release or reject raw materials, intermediates, packaging and labelling materials;

3. Reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution;

4. Making sure that critical deviations are investigated and resolved;

5. Approving all specifications and master production instructions;

6. Approving all procedures impacting the quality of intermediates or APIs;

7. Making sure that internal audits (self-inspections) are performed;

8. Approving intermediate and API contract manufacturers;

9. Approving changes that potentially impact intermediate or API quality;

10. Reviewing and approving validation protocols and reports;

11. Making sure that quality related complaints are investigated and resolved;

12. Making sure that effective systems are used for maintaining and calibrating critical equipment;

13. Making sure that materials are appropriately tested and the results are reported;

14. Making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate; and

15. Performing product quality reviews (as defined in Section 2.6).

2.4 Responsibility for Production Activities

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

1. Preparing, reviewing, approving and distributing the instructions for the production of intermediates or APIs according to written procedures;

2. Producing APIs and, when appropriate, intermediates according to pre- approved instructions;

3. Reviewing all production batch records and ensuring that these are completed and signed;

4. Making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded;

5. Making sure that production facilities are clean and when appropriate disinfected;

6. Making sure that the necessary calibrations are performed and records kept;

7. Making sure that the premises and equipment are maintained and records kept;

8. Making sure that validation protocols and reports are reviewed and approved;

9. Evaluating proposed changes in product, process or equipment; and

10. Making sure that new and, when appropriate, modified facilities and equipment are qualified.

2.5 Internal Audits (Self Inspection)

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

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

2.6 Product Quality Review

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

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

- A review of all quality-related returns, complaints and recalls; and
- A review of adequacy of corrective actions.

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

3. PERSONNEL

3.1 Personnel Qualifications

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

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

3.12 Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

3.2 Personnel Hygiene

3.20 Personnel should practice good sanitation and health habits.

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

3.22 Personnel should avoid direct contact with intermediates or APIs.

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

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

3.3 Consultants

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

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

4. BUILDINGS AND FACILITIES

4.1 Design and Construction

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

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

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

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

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

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

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

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

4.2 Utilities

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

4.21 Adequate ventilation, air filtration and exhaust systems should be provided, where

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

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

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

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

4.3 Water

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

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

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

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

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

4.4 Containment

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

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

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

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

APIs.

4.5 Lighting

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

4.6 Sewage and Refuse

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

4.7 Sanitation and Maintenance

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

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

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

5. PROCESS EQUIPMENT

5.1 Design and Construction

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

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

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

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

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

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

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

5.2 Equipment Maintenance and Cleaning

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

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

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

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

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

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

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

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

5.3 Calibration

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

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

5.32 Records of these calibrations should be maintained.

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

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

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

5.4 Computerized Systems

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

5.41 Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.

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

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

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

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

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

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

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

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

6. DOCUMENTATION AND RECORDS

6.1 Documentation System and Specifications

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

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

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

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

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

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

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

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

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

6.2 Equipment Cleaning and Use Record

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

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

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

6.30 Records should be maintained including:

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

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

6.4 Master Production Instructions (Master Production and Control Records)

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

6.41 Master production instructions should include:

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

- Where appropriate, special notations and precautions to be followed, or cross-references to these; and
- The instructions for storage of the intermediate or API to assure its suitability for use, including the labelling and packaging materials and special storage conditions with time limits, where appropriate.

6.5 Batch Production Records (Batch Production and Control Records)

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

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

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

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

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

6.6 Laboratory Control Records

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

- A description of samples received for testing, including the material name or source,

batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing;

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

6.61 Complete records should also be maintained for:

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

6.7 Batch Production Record Review

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

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

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

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

7. MATERIALS MANAGEMENT

7.1 General Controls

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

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

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

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

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

7.2 Receipt and Quarantine

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

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

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

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

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

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

7.3 Sampling and Testing of Incoming Production Materials

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

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

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

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

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

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

7.4 Storage

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

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

7.42 Materials should be stored under conditions and for a period that have no adverse affect on their quality, and should normally be controlled so that the oldest stock is used first.

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

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

7.5 Re-evaluation

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

8. PRODUCTION AND IN-PROCESS CONTROLS

8.1 Production Operations

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

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

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

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

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

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

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

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

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

8.2 Time Limits

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

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

8.3 In-process Sampling and Controls

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

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

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

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

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

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

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

8.4 Blending Batches of Intermediates or APIs

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

8.41 Out-Of-Specification batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

8.42 Acceptable blending operations include but are not limited to:

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

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

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

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

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

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

8.5 Contamination Control

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

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

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

9. PACKAGING AND IDENTIFICATION LABELLING OF APIs AND INTERMEDIATES

9.1 General

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

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

9.12 Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.

9.2 Packaging Materials

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

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

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

9.3 Label Issuance and Control

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

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

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

9.33 Obsolete and out-dated labels should be destroyed.

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

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

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

9.4 Packaging and Labelling Operations

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

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

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

9.43 If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, and special transport conditions and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.

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

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

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

10. STORAGE AND DISTRIBUTION

10.1 Warehousing Procedures

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

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

10.2 Distribution Procedures

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

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

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

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

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

11. LABORATORY CONTROLS

11.1 General Controls

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

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

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

11.13 Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities, and

residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.

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

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

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

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

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

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

11.2 Testing of Intermediates and APIs

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

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

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

11.23 Appropriate microbiological tests should be conducted on each batch of intermediate and

API where microbial quality is specified.

11.3 Validation of Analytical Procedures - see Section 12.

11.4 Certificates of Analysis

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

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

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

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

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

11.5 Stability Monitoring of APIs

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

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

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

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

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

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

testing) can be considered.

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

11.6 Expiry and Retest Dating

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

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

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

(1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale; and

(2) the quality of the API represents the material to be made on a commercial scale.

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

11.7 Reserve/Retention Samples

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

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

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

12. VALIDATION

12.1 Validation Policy

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

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

- Defining the API in terms of its critical product attributes;
- Identifying process parameters that could affect the critical quality attributes of the API;

- Determining the range for each critical process parameter expected to be used during routine manufacturing and process control.

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

12.2 Validation Documentation

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

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

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

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

12.3 Qualification

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

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

12.4 Approaches to Process Validation

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

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

12.42 Prospective validation should normally be performed for all API processes as defined in 12.12. Prospective validation performed on an API process should be

completed before the commercial distribution of the final drug product manufactured from that API.

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

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

(1) Critical quality attributes and critical process parameters have been identified;

(2) Appropriate in-process acceptance criteria and controls have been established;

(3) There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability; and

(4) Impurity profiles have been established for the existing API.

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

12.5 Process Validation Program

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

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

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

12.6 Periodic Review of Validated Systems

12.60 Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently

producing material meeting its specifications, there is normally no need for revalidation.

12.7 Cleaning Validation

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

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

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

12.73 Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).

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

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

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

12.8 Validation of Analytical Methods

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

12.81 Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation

performed should reflect the purpose of the analysis and the stage of the API production process.

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

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

13. CHANGE CONTROL

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

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

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

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

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

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

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

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

14. REJECTION AND RE-USE OF MATERIALS

14.1 Rejection

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

14.2 Reprocessing

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

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

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

14.3 Reworking

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

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

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

14.4 Recovery of Materials and Solvents

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

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

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

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

14.5 Returns

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

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

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

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

15. COMPLAINTS AND RECALLS

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

15.11 Complaint records should include:

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

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

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

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

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

16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

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

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

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

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

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

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

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

17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS AND RELABELLERS

17.1 Applicability

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

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

17.2 Traceability of Distributed APIs and Intermediates

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

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

17.3 Quality Management

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

17.4 Repackaging, Relabelling and Holding of APIs and Intermediates

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

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

17.5 Stability

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

17.6 Transfer of Information

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

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

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

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

17.7 Handling of Complaints and Recalls

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

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

17.72 Where a complaint is referred to the original API or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, repackers, or relabellers should

include any response received from the original API or intermediate manufacturer (including date and information provided).

17.8 Handling of Returns

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

18. SPECIFIC GUIDANCE FOR APIs MANUFACTURED BY CELL CULTURE/FERMENTATION

18.1 General

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

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

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

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

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

18.15 Appropriate equipment and environmental controls should be used to minimize the risk of

contamination. The acceptance criteria for quality of the environment and the frequency of monitoring should depend on the step in production and the production conditions (open, closed, or contained systems).

18.16 In general, process controls should take into account:

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

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

18.2 Cell Bank Maintenance and Record Keeping

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

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

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

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

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

18.3 Cell Culture/Fermentation

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

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

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

18.33 Critical operating parameters (for example temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process.

Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.

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

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

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

18.37 Records of contamination events should be maintained.

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

18.4 Harvesting, Isolation and Purification

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

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

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

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

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

18.5 Viral Removal/Inactivation Steps

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

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

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

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

19. APIs FOR USE IN CLINICAL TRIALS

19.1 General

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

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

19.2 Quality

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

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

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

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

19.24 Process and quality problems should be evaluated.

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

19.3 Equipment and Facilities

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

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

19.4 Control of Raw Materials

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

19.41 In some instances, the suitability of a raw material can be determined before use based

on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

19.5 Production

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

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

19.6 Validation

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

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

19.7 Changes

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

19.8 Laboratory Controls

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

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

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

19.9 Documentation

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

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

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

20. GLOSSARY

Acceptance Criteria

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

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

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

API Starting Material

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

Batch (or Lot)

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

Batch Number (or Lot Number)

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

Bioburden

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

Calibration

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

Computer System

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

Computerized System

A process or operation integrated with a computer system.

Contamination

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

Contract Manufacturer

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

Critical

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

Cross-Contamination

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

Deviation

Departure from an approved instruction or established standard.

Drug (Medicinal) Product

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

Drug Substance

See Active Pharmaceutical Ingredient

Expiry Date (or Expiration Date)

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

Impurity

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

Impurity Profile

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

In-Process Control (or Process Control)

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

Intermediate

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

Lot

See Batch

Lot Number see Batch Number See Batch

Number **Manufacture**

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

Material

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

Mother Liquor

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

Packaging Material

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

Procedure

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

Process Aids

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

Process Control

See In-Process Control

Production

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

Qualification

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

Quality Assurance (QA)

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

Quality Control (QC)

Checking or testing that specifications are met.

Quality Unit(s)

An organizational unit independent of production which fulfils both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine

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

Raw Material

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

Reference Standard, Primary

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

Reference Standard, Secondary

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

Reprocessing

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

Retest Date

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

Reworking

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

Signature (signed) See definition

for signed **Signed (signature)**

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

Solvent

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

Specification

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

Validation

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

Validation Protocol

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

Yield, Expected

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

Yield, Theoretical

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

PART 3

GUIDELINES ON THE PREPARATION OF A SITE MASTER FILE

1. INTRODUCTION

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

1.2. When submitted to the Ministry of Health, the Site Master File should provide clear information on the manufacturer's GMP related activities that can be useful in general supervision and in the efficient planning and undertaking of GMP inspections.

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

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

2. PURPOSE

The purpose of these guidelines is to help the manufacturer of medicinal products in the preparation of a Site Master File that is useful to the Ministry of Health in planning and conducting GMP inspections.

3. SCOPE

These guidelines apply to the preparation and content of the Site Master File. Manufacturers should refer to the Ministry of Health to establish whether it is mandatory for manufacturers of medicinal products to prepare a Site Master File.

These guidelines apply for all kind of manufacturing operations such as production, packaging and labelling, testing, relabeling and repackaging of all types of medicinal products. The outlines of this guide could also be used in the preparation of a Site Master File or corresponding document by Blood and Tissue Establishments and manufacturers of active pharmaceutical ingredients.

4. CONTENT OF SITE MASTER FILE

Refer to the Annex for the format to be used.

ANNEX: CONTENT OF SITE MASTER FILE

1. GENERAL INFORMATION ON THE MANUFACTURER

1.1. Contact information on the manufacturer

- Name and official address of the manufacturer
- Names and street addresses of the site, buildings and production units located on the site
- Contact information of the manufacturer including 24-hours telephone number of the contact personnel in the case of product defects or recalls
- Identifying information regarding the location of the manufacturing site (e.g. GPS details, or any other geographic location system)

1.2. Authorised pharmaceutical manufacturing activities of the site

- Copy of the valid manufacturing authorisation issued by the Ministry of Health should be submitted in Appendix 1. If manufacturing authorizations are not issued yet, this should be stated.
- Brief description of manufacture, import, export, distribution and other activities as authorized by the Ministry of Health; including foreign authorities with authorized dosage forms/activities, respectively, where not covered by the manufacturing authorization;
- Type of products currently manufactured on-site, if not covered by Appendix 1 (list in Appendix 2).
- A list including the dates of inspections and brief information on the results of inspections of the site by the Ministry of Health. If inspections are conducted by foreign authorities, a list of GMP inspections of the site within the last 5 years; including dates and name/country of the Competent Authority having performed the inspection. A copy of current GMP certificate (Appendix 3) should be included, if available.

1.3. Any other manufacturing activities carried out on the site

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

2. QUALITY MANAGEMENT SYSTEM OF THE MANUFACTURER

2.1. Quality management system of the manufacturer

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

2.2. Release procedure of finished products

- Detailed description of qualification requirements (education and work experience) of the authorised persons/qualified persons responsible for batch certification and releasing procedures
- General description of batch certification and releasing procedure

- Role of Authorised Person / Qualified Person in quarantine and release of finished products and in assessment of compliance with the marketing authorisation
- The arrangements between authorised persons/qualified persons when several authorised persons/qualified persons are involved
- Statement on whether the control strategy employs Process Analytical Technology (PAT) and/or Real Time Release or Parametric Release

2.3. Management of suppliers and contractors

- A brief summary of the establishment/knowledge of supply chain and the external audit program
- Brief description of the qualification system of contractors, manufacturers of active pharmaceutical ingredients and other critical materials suppliers
- The manufacturer is responsible for demonstrating specific measures taken to prevent the transmission of spongiform encephalopathy from animals, and all steps of manufacturing and materials used are in compliance with the regulations on the minimisation of the risks for transmission of animal spongiform encephalopathy (BSE/TSE) via medicinal products. Compliance with the said regulations may be demonstrated with a certification on compliance with the relevant monograph of the European Pharmacopeia, or with a submission to the Ministry of Health including the scientific data demonstrating the compliance with the said monograph.
- Measures adopted where counterfeit/falsified products, bulk products (i.e. unpacked tablets), active pharmaceutical ingredients or excipients are suspected or identified
- Use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis
- List of contract manufacturers and laboratories including the addresses and contact information and flow charts of supply-chains for outsourced manufacturing and quality control activities; e.g. sterilization of primary packaging material for aseptic processes, testing of starting raw-materials etc, should be presented in Appendix 4
- Brief overview of the responsibility sharing between the contract giver and acceptor with respect to compliance with the Marketing Authorization (where not included under 2.2)

2.4. Quality Risk Management

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

2.5. Product Quality Reviews

- Brief description of methodologies used

3. PERSONNEL

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

4. FACILITIES AND EQUIPMENT

4.1. Facilities

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

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

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

4.1.2. Brief description of water systems

- Quality references of water produced
- Schematic drawings of the systems in Appendix 7

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

4.2. Equipment

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

4.2.2. Cleaning and sanitation

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

4.2.3. GMP critical computerised systems

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

5. DOCUMENTATION

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

6. PRODUCTION

6.1. Types of products

(References to Appendix 1 or 2 can be made):

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

6.2. Process validation

- Brief description of general policy for process validation
- Policy for reprocessing or reworking

6.3. Material and warehouse management

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

7. QUALITY CONTROL

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

8. DISTRIBUTION, COMPLAINTS, PRODUCT DEFECTS AND RECALLS

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

- Types (wholesale licence holders, manufacturing licence holders, etc.) and locations (local, EU/EEA, USA, etc) of the companies to which the products are shipped from the site.

- Description of the system used to verify that each customer / recipient is authorized by the Ministry of Health to receive medicinal products from the manufacturer.
- Brief description of the system to ensure appropriate environmental conditions during transit, (e.g. temperature monitoring/ control).
- Arrangements for product distribution and methods by which product traceability is maintained.
- Measures taken to prevent manufacturers' products to fall in the illegal supply chain.

8.2. Complaints, product defects and recalls

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

9. SELF INSPECTION

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

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

ANNEX-1

MANUFACTURE OF STERILE MEDICINAL PRODUCTS

PRINCIPLE

The manufacture of sterile products is subject to special requirements in order to minimise 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:

Grade	Maximum permitted number of particles/m³ equal to or greater than			
	At rest		In operation	
	0.5µm	5.0µm	0.5µm	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 1m³ 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 and in operation) the airborne particle classification is ISO 7 and ISO 8 respectively. For Grade D (at rest) the airborne particle classification is ISO 8. For

classification purposes EN/ISO 14644-1 methodology defines both the minimum number of sample locations and the sample size based on the class limit of the largest considered particle size and the method of evaluation of the data collected.

6. Portable particle counters with a short length of sample tubing 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 should 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
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 (diam. 90 mm), cfu/4	Contact plates (diam. 55 mm),	Glove print 5 fingers
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 minimise 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 minimise 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 minimise 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 minimise 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 particlegenerating 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 minimise 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 minimise 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 (or other relevant) 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 of the results should be kept.

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 sterilising 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 minimise 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 sterilisation 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) for 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 MEDICINAL SUBSTANCES AND PRODUCTS FOR HUMAN USE

SCOPE

The methods employed in the manufacture of biological medicinal substances and products are a critical factor in shaping the appropriate regulatory control. Biological medicinal substances and products can be defined therefore largely by reference to their method of manufacture. This annex provides guidance on the full range of medicinal substances and products defined as biological.

This annex is divided into two main parts:

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

b) Part B contains further guidance on selected types of biological medicinal substances and products.

This annex, along with several other annexes of the Guide to GMP, provides guidance which supplements that in Part I and in Part II of the 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. For some types of product (e.g. Advanced Therapy Medicinal Products (ATMP) cell-based products) all manufacturing steps need to be conducted aseptically.

b) Type of product - this annex provides guidance on the full range of medicinal substances and products defined as biological.

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 the Guide, the level of GMP increases in detail from early to later steps in the manufacture of biological substances but GMP principles should always be adhered to. The inclusion of some early steps of manufacture within the scope of the annex does not imply that those steps will be routinely subject to inspection by the authorities. Antibiotics are not defined or included as biological 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 12 and for non-transgenic plant products in Annex 5.

In certain cases, other legislation may be applicable to the starting materials for biologicals:

(a) For tissue and cells used for industrially manufactured products (such as pharmaceuticals), the donation, procurement and testing of tissue and cells may be covered by national legislation.

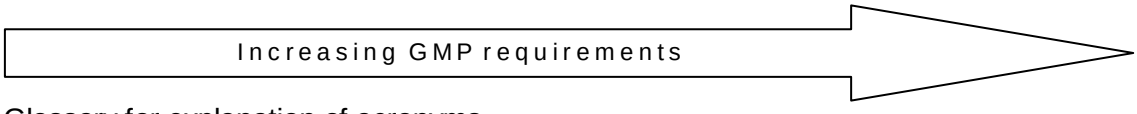
(b) Where blood or blood components are used as starting materials for ATMPs, national legislation may provide the technical requirements for the selection of donors and the collection and testing of blood and blood components[1].

(c) The manufacture and control of genetically modified organisms needs to comply with local and national requirements. Appropriate containment should be established and maintained in facilities where any genetically modified micro-organism is handled[2]. Advice should be obtained according to national legislation in order to establish and maintain the appropriate Biological Safety Level including measures to prevent cross contamination. There should be no conflicts with GMP requirements.

[1] See National Guideline on Blood and Blood Products.
[2] See Directive 2009/41/EC.

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, ATMPs immunosera	Collection of plant, organ, tissue or fluid[3]	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[4], 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 Gene Therapy (viral and non-viral vectors, plasmids)	Establishment & maintenance of MCB and WCB, MSL, WSL	Cell culture and /or fermentation	Isolation, purification, modification	Formulation, filling
4. Animal sources: transgenic	Recombinant proteins, ATMPs	Master and working transgenic bank	Collection, cutting, mixing, and/or initial processing	Isolation, purification and modification	Formulation, filling
5. Plant sources: transgenic	Recombinant proteins, vaccines, allergen	Master and working transgenic bank[6]	Growing, harvesting[5]	Initial extraction, isolation, purification, modification	Formulation, filling
6. Human sources	Urine derived enzymes, hormones	Collection of fluid	Mixing, and/or initial processing	Isolation and purification	Formulation, filling
7. Human and/or animal sources	Gene therapy: genetically modified cells	Donation, procurement and testing of starting tissue / cells[8]	Manufacture vector[7] and cell purification and processing,	Ex-vivo genetic modification of cells, Establish MCB, WCB or primary cell lot	Formulation, filling
	Somatic cell therapy	Donation, procurement and testing of starting tissue / cells[8]	Establish MCB, WCB or primary cell lot or cell pool	Cell isolation, culture purification, combination with non-cellular components	Formulation, combination, fill
	Tissue engineered products	Donation, procurement and testing of starting tissue / cells[8]	Initial processing, isolation and purification, establish MCB, WCB, primary cell lot or cell pool	Cell isolation, culture, purification, combination with non-cellular components	Formulation, combination, fill



See Glossary for explanation of acronyms.

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[3] See section B1 for the extent to which GMP principles apply.

[4] See section on 'Seed lot and cell bank system' for the extent to which GMP applies.

[5] Good Agricultural Practice may be applied to growing, harvesting and initial processing in open fields.

[6] For principles of GMP apply, see explanatory text in 'Scope'.

[7] Where these are viral vectors, the main controls are as for virus manufacture (row 2).

[8] In accordance with Regulation on Quality and Safety of Human Tissues and Cells and Related Establishments and Communiqué on Registration of Human Tissue and Cell Products and Establishments Conducting Manufacturing, Import, Export, Storage and Distribution Activities.

PRINCIPLE

The manufacture of biological medicinal products involves certain specific considerations arising from the nature of the products and the processes. The ways in which biological medicinal products are 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 medicinal substances and products involves biological processes and materials, such as cultivation of cells or extraction of material from living organisms. These biological processes may display inherent variability, so 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 their 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, many products are 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. For biological materials that cannot be sterilized (e.g. by filtration), processing must be conducted aseptically to minimise the introduction of contaminants. 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 medicinal substances and products.

Biological medicinal products which incorporate human tissues or cells, such as certain ATMPs must comply with national requirements for the donation, procurement and testing stages[9]. Collection and testing of this material must be done in accordance with an appropriate quality system and in accordance with applicable

[9] Regulation on Quality and Safety of Human Tissues and Cells and Related Establishments and Communiqué on Registration of Human Tissue and Cell Products and Establishments Conducting Manufacturing, Import, Export, Storage and Distribution Activities.

national requirements[10]. Furthermore, national requirements[11] on traceability apply from the donor (while maintaining donor confidentiality) through stages applicable at the Tissue Establishment and then continued under medicines legislation through to the institution where the product is used.

Biological medicinal substances and products must comply with the applicable national guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products.

PART A. GENERAL GUIDANCE

PERSONNEL

1. Personnel (including those concerned with cleaning, maintenance or quality control) employed in areas where biological medicinal products are manufactured and tested should receive training, and periodic retraining, specific to the products manufactured and to their work, including any specific 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 X-ray. 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 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.

PREMISE 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 product and the production step, bearing in mind the level of contamination of the starting materials and the risks to the product. The environmental monitoring programme in addition to Annex 1 should be supplemented by the

[10] [11] Regulation on Quality and Safety of Human Tissues and Cells and Related Establishments and Communiqué on Registration of Human Tissue and Cell Products and Establishments Conducting Manufacturing, Import, Export, Storage and Distribution Activities.

inclusion of methods to detect the presence of specific microorganisms (e.g. host organism, 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. Although contamination is likely to become evident during processes such as fermentation and cell culture, prevention of contamination is more appropriate than detection and removal. In fact, the environmental monitoring and material bioburden testing programs are intended to verify a state of control. 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, manipulations during the manufacture of ATMPs) 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 requirements from the appropriate sections of Annex 1[12] 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, until inactivation. Dedicated production area should be used for the manufacture of pathogenic organisms capable of causing severe human disease[13].

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 using QRM principles:

   (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 (e.g. cell-based products), factors such as the health status of donors and the risk of total loss of product from and/or for specific patients should be taken into account when considering the acceptance of concurrent working during development of the control strategy.

   (c) Live organisms and spores (where relevant) are prevented from entering non-related areas or equipment. Control measures to remove the organisms and spores before the subsequent manufacture of other products, these control measures should also take the HVAC system into account. Cleaning and decontamination for the removal of the organisms and spores should be validated.

   (d) Environmental monitoring, specific for the micro-organism being manufactured, is also 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

[12] GMP Guide.

[13] See Regulation on Prevention the Risk of Exposure to Biological Agents on the matter.

(e.g. airborne particle monitoring) in areas handling live and/or spore forming organisms.

(e) 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).

(f) Campaign-based manufacturing followed by validated cleaning and decontamination procedures.

9. For finishing 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 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 safety.

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 of the live organism or cell 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.

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[14] Formulation, filling and packaging

[15] See main GMP Glossary on ‘Containment’.

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. Compliance with local regulations is required to minimize the risk of contamination of the external environment according to the risk associated with the biohazardous nature of waste materials.

18. Due to the variability of biological products or processes, relevant/critical additives or ingredients may have to be measured or weighed during the production process. In these cases, stocks of these substances 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. Materials must be stored appropriately.

ANIMALS

19. A wide range of animal species are used in the manufacture of a number of biological medicinal products or starting materials. 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 tissues and cells derived post-mortem and from establishments such as abattoirs: examples include xenogeneic cells from animal tissues and cells, feeder cells to support the growth of some ATMPs, 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 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 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 medicinal substance(s) or product(s) in which the 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 (where applicable) to establish the last negative donation. The withdrawal period of therapeutic agents used to treat source animals must be documented and used to determine the removal of those animals from the programme for defined periods.

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 pharmacopoeial 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 national requirements for animal quarters, care and quarantine[16]. Housing for animals used in production and control of biological 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 appropriately identified to prevent any risk of mix up and to control all identified hazards.

DOCUMENTATION

26. Specifications for biological starting 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 somatic cells in the context of ATMPs. 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[17]. Traceability records[18] must be retained for 30 years after the expiry date of the product. Particular care should be taken to maintain the traceability of products for special use cases, such as donor-matched cells. National requirements apply to blood components when they are used as supportive or raw material in the manufacturing process of medicinal products[19]. For ATMPs, traceability requirement regarding human cells including haematopoietic cells must comply with the principles laid down in national

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16 See Directive 201/63/EC.

17 18 See Regulation on Quality and Safety of Human Tissues and Cells and Related Establishments and Communiqué on Registration of Human Tissue and Cell Products and Establishments Conducting Manufacturing, Import, Export, Storage and Distribution Activities.

19 See National Guideline on Blood and Blood Products.

legislation[20]. The arrangements necessary to achieve the traceability and retention period should be incorporated into technical agreements between the responsible parties.

PRODUCTION

29. Given the variability inherent in many biological substances and 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 cell based ATMPs 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 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 6 and for biological substances in Part II.

32. The risk of contamination of starting 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 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 materials and on the aseptic manufacturing process, particularly for cell-based products, where final sterilisation is generally not possible and the ability to remove microbial

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20 See Regulation on Quality and Safety of Human Tissues and Cells and Related Establishments and Communiqué on Registration of Human Tissue and Cell Products and Establishments Conducting Manufacturing, Import, Export, Storage and Distribution Activities.

by-products is limited, assume greater importance. 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 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 and carefully controlled, they should be removed from the manufacturing process at the stage specified in the MA or CTA. [21]

36. For human tissues and cells used as starting materials for biological medicinal products:

    (a) Their procurement, donation and testing is regulated in some countries[22]. Such supply sites must hold appropriate approvals from the national competent authority(ies) which should be verified as part of starting material supplier management.

    (b) Where such human cells or tissues are imported they must meet equivalent national standards of quality and safety[23]. The traceability and serious adverse reaction and serious adverse event notification requirements may be set out in national legislation[24].

    (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, e.g. to derive early cell lines or banks prior to establishing a Master Cell Bank, MCB[25].

    (d) Tissue and cells are released by the Responsible Person 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.

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21 Some situations in which antibiotic use may be justified include maintenance of plasmids in expression systems and in fermentation. Generally, antibiotics used in humans should be avoided because of the potential development of antibiotic resistant strains. Additionally, the use of antibiotics is not an effective mechanism to control microbial contamination.

22, 23, 24, 25 See Regulation on Quality and Safety of Human Tissues and Cells and Related Establishments and Communiqué on Registration of Human Tissue and Cell Products and Establishments Conducting Manufacturing, Import, Export, Storage and Distribution Activities.

(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.

(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 responsibilities of each party, including the RP.

37. With regard to gene therapy[26]:

(a) For products consisting of viral vectors, the starting materials are the components from which the viral vector is obtained, i.e. the master virus seed or the plasmids to transfect the packaging cells and the MCB of the packaging cell line.

(b) For products consisting of plasmids, non-viral vectors and genetically modified micro-organisms other than viruses or viral vectors, the starting materials are the components used to generate the producing cell, i.e. the plasmid, the host bacteria and the MCB of the recombinant microbial cells.

(c) For genetically modified cells, the starting materials are the components used to obtain the genetically modified cells, i.e. the starting materials to manufacture the vector and the human or animal cell preparations.

(d) The principles of GMP apply from the bank system used to manufacture the vector or plasmid used for gene transfer.

38. 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[27], including compliance with national requirements for human cells.

SEED LOT AND CELL BANK SYSTEM

39. 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. Such a system may not be applicable to all types of ATMPs.

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

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26 See section 3.2 of Directive 2009/120/EC.

27 See Regulation on Quality and Safety of Human Tissues and Cells and Related Establishments and Communiqué on Registration of Human Tissue and Cell Products and Establishments Conducting Manufacturing, Import, Export, Storage and Distribution Activities.

41. 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 pharmacopoeial monographs will apply[28].

42. 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.

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

44. Cell based medicinal products are often generated from a cell stock obtained from limited number of passages. In contrast with the two tiered system of Master and Working cell banks, the number of production runs from a cell stock is limited by the number of aliquots obtained after expansion and does not cover the entire life cycle of the product. Cell stock changes should be covered by a validation protocol.

45. 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.

46. 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.

47. The storage and handling conditions for stocks should be managed according to the same procedures and parameters. Once containers are removed from

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28 See Ph Eur monograph 2005;153 “Vaccines for human use”.

the seed lot / cell bank management system, the containers should not be returned to stock.

OPERATING PRINCIPLES

48. 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 of the final product.

49. 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.

50. A control strategy for the entry of articles and materials into production areas should be based on QRM principles to minimise the risk of contamination. 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.

51. 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.

52. 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.

53. 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.

54. Centrifugation and blending of products can lead to aerosol formation and containment of such activities to minimise cross-contamination is necessary.

55. Accidental spillages, especially of live organisms, must be dealt with quickly and safely. Validated 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.

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

57. The methods used for sterilisation, disinfection, virus removal or inactivation should be validated[29].

58. 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.

59. 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.

60. 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.

61. Where ionising radiation is used in the manufacture of medicinal products, Annex 10 should be consulted for further guidance.

62. 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.

63. Activities in handling containers, which have 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. This risk assessment should take into consideration the viability of such organisms and their biological classification.

64. Care should be taken in the preparation, printing, storage and application of labels, including any specific text for patient-specific products or signifying the use of genetic engineering of the contents on the primary container and secondary packaging. In the case of products used for autologous use, the unique patient identifier and the statement “for autologous use only” should be indicated on the immediate label.

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29 See EMA, CHMP guidance.

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

66. Where donor and/or animal health information becomes available after procurement, which affects product quality, it should be taken into account in recall procedures.

QUALITY CONTROL

67. In-process controls have a greater importance in ensuring the consistency of the quality of biological 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.

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

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

70. For cell-based ATMPs, 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.

71. For products with a short shelf life, 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 input 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 possible due to their short shelf life, alternative methods of obtaining equivalent data to permit 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 - before and after full end process analytical test results are available:

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

b) Assessment of the final analytical tests and other information available before end product dispatch for final product certification by the Responsible Person.

c) 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 after product dispatch. Such events should be fully investigated and the relevant corrective and preventative actions taken to prevent recurrence documented.

A procedure should describe those measures which will be taken by the Responsible Person if unsatisfactory test results are obtained after dispatch.

PART B. SPECIFIC GUIDANCE ON SELECTED PRODUCT TYPES

B1. ANIMAL SOURCED PRODUCTS

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 appropriate pharmacopoeial monographs, including the need for specific tests at defined stages. Documentation to demonstrate the supply chain traceability[30] 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 and control measures when compiling their assessment of risk and mitigation factors. Such organisations include the World Organisation for Animal Health (OIE, Office International des Epizooties[31]). 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 stringent standards. Account should be taken of reports from national regulatory organisations[32] which verify compliance with the requirements of food, safety, quality and veterinary and plant health legislation.

3. Control measures for the pharmaceutical raw materials at establishments such as abattoirs should include appropriate elements of Quality Management System to assure a satisfactory level of operator training, materials traceability, control and consistency. These measures may be drawn from sources outside GMP Guide but should be shown to provide equivalent levels of control.

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30 See GMP Guide Chapter 5.

31 http://www.oie.int/eng/en_index.htm

32 Ministry of Food, Agriculture and Livestock.

4. Control measures for 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 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.

6. Cells, tissues and organs intended for the manufacture of xenogeneic cell-based medicinal products should be obtained only from animals that have been bred in captivity (barrier facility) specifically for this purpose and under no circumstances should cells, tissues and organs from wild animals or from abattoirs be used. Tissues of founder animals similarly should not be used. The health status of the animals should be monitored and documented.

7. For xenogeneic cell therapy products appropriate guidance in relation to procurement and testing of animal cells should be followed[33].

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 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.

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33 See EMA Guideline document on xenogeneic cell-based medicinal products.

B.3 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.

B.4 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 product and the hold times must be validated.

3. Vessels containing inactivated product 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 the manufacturing instructions or the batch record.

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.

B.5 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 harvests, 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 cycle should be verified that these are within approved limits.

3. The manufacturing conditions for the preparation of antibody sub-fragments (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'[34] should be taken into account when drawing up such criteria.

B9. GENE THERAPY PRODUCTS[35]

There are potentially 2 types of GT products (vectors and genetically modified cells) and both are within the scope of the guidance in this section. For cell based GT products, some aspects of guidance in section B10 may be applicable.

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[34] Regulation on Good Agricultural Practice and EMA, WHO documents.

[35] Part IV of Regulation on Registration of Human Medicinal Products contains a definition of gene therapy (GT) medicinal products.

1. Since the cells used in the manufacture of gene therapy products are obtained either from humans (autologous or allogeneic) or animals (xenogeneic), there is a potential risk of contamination by adventitious agents. Special considerations must be applied to the segregation of autologous materials obtained from infected donors. The robustness of the control and test measures for such starting materials, cryoprotectants, culture media, cells and vectors should be based on QRM principles and in line with the MA or CTA. Established cell lines used for viral vector production and their control and test measures should similarly be based on QRM principles. Virus seed lots and cell banking systems should be used where relevant.

2. Factors such as the nature of the genetic material, type of (viral or non-viral) vector and type of cells have a bearing on the range of potential impurities, adventitious agents and cross-contaminations that should be taken into account as part of the development of an overall strategy to minimise risk. This strategy should be used as a basis for the design of the process, the manufacturing and storage facilities and equipment, cleaning and decontamination procedures, packaging, labelling and distribution.

3. The manufacture and testing of gene therapy medicinal products raises specific issues regarding the safety and quality of the final product and safety issues for recipients and staff. A risk based approach for operator, environment and patient safety and the implementation of controls based on the biological hazard class should be applied. Legislated local and, if applicable, international safety measures should be applied.

4. Personnel (including QC and maintenance staff) and material flows, including those for storage and testing (e.g. starting materials, in-process and final product samples and environmental monitoring samples), should be controlled on the basis of QRM principles, where possible utilising unidirectional flows. This should take into account movement between areas containing different genetically modified organisms and areas containing non-genetically-modified organisms.

5. Any special cleaning and decontamination methods required for the range of organisms being handled should be considered in the design of facilities and equipment. Where possible, the environmental monitoring programme should be supplemented by the inclusion of methods to detect the presence of the specific organisms being cultivated.

6. Where replication limited vectors are used, measures should be in place to prevent the introduction of wild-type viruses, which may lead to the formation of replication competent recombinant vectors.

7. An emergency plan for dealing with accidental release of viable organisms should be in place. This should address methods and procedures for containment, protection of operators, cleaning, decontamination and safe return to use. An assessment of impact on the immediate products and any others in the affected area should also be made.

8. Facilities for the manufacture of viral vectors should be separated from other areas by specific measures. The arrangements for separation should be demonstrated to be effective. Closed systems should be used wherever

possible, sample collection additions and transfers should prevent the release of viral material.

9. Concurrent manufacture of different viral gene therapy vectors in the same area is not acceptable. Concurrent production of non-viral vectors in the same area should be controlled on the basis of QRM principles. Changeover procedures between campaigns should be demonstrated to be effective.

10. A description of the production of vectors and genetically modified cells should be available in sufficient detail to ensure the traceability of the products from the starting material (plasmids, gene of interest and regulatory sequences, cell banks, and viral or non viral vector stock) to the finished product.

11. Shipment of products containing and/or consisting of GMO should conform to appropriate legislation.

12. The following considerations apply to the ex-vivo gene transfer to recipient cells:

    (a) These should take place in facilities dedicated to such activities where appropriate containment arrangements exist.

    (b) Measures (including considerations outlined under paragraph 10 in Part A) to minimise the potential for cross-contamination and mix-up between cells from different patients are required. This should include the use of validated cleaning procedures. The concurrent use of different viral vectors should be subject to controls based on QRM principles. Some viral vectors (e.g. Retro- or Lenti-viruses) cannot be used in the manufacturing process of genetically modified cells until they have been shown to be devoid of replication-competent contaminating vector.

    (c) Traceability requirements must be maintained. There should be a clear definition of a batch, from cell source to final product container(s).

    (d) For products that utilise non-biological means to deliver the gene, their physico-chemical properties should be documented and tested.

B.10 SOMATIC AND XENOGENEIC CELL THERAPY PRODUCTS AND TISSUE ENGINEERED PRODUCTS[36]

For genetically modified cell based products that are not classified as GT products, some aspects of guidance in section B9 may be applicable.

1. Use should be made, where they are available, of authorised sources (i.e. licensed medicinal products or medical devices which have gone through a conformity assessment procedure[37]) of additional substances (such as cellular products, bio-molecules, bio-materials, scaffolds, matrices).

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[36] Annex I, Part IV (2) of Regulation on Registration of Human Medicinal Products contains a definition of somatic cell therapy (SCT) medicinal products and the definition of a tissue engineered medicinal product is given in Article 2 of Regulation 1394/2007/EC.

[37] Devices are marked “CE”.

2. Where devices, including custom-made devices, are incorporated as part of the products:

   (a) There should be written agreement between the manufacturer of the medicinal product and the manufacturer of the medical device, which should provide enough information on the medical device to avoid alteration of its properties during manufacturing of the ATMP. This should include the requirement to control changes proposed for the medical device.

   (b) The technical agreement should also require the exchange of information on deviations in the manufacture of the medical device.

3. Since somatic cells are obtained either from humans (autologous or allogeneic) or animals (xenogeneic), there is a potential risk of contamination by adventitious agents. Special considerations must be applied to the segregation of autologous materials obtained from infected donors or related to cell pooling. The robustness of the control and test measures put in place for these source materials should be ensured. Animals from which tissues and cells are collected should be reared and processed according to the principles defined in the relevant guidelines[38].

4. Careful attention should be paid to specific requirements at any cryopreservation stages, e.g. the rate of temperature change during freezing or thawing. The type of storage chamber, placement and retrieval process should minimise the risk of cross-contamination, maintain the quality of the products and facilitate their accurate retrieval. Documented procedures should be in place for the secure handling and storage of products with positive serological markers.

5. 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 consider the detection of fastidious organism.

6. Where relevant, a stability-monitoring programme should be in place together with reference and retain samples in sufficient quantity to permit further examination.

GLOSSARY TO ANNEX 2

Entries are only included where the terms are used in Annex 2 and require further explanation. Defintions which already exist in legislation are cross-referenced only.

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

Advance Therapeutic Medicinal Products (ATMP). ATMP means any of the following medicinal products for human use: gene therapy medicinal products, somatic cell therapy medicinal products and tissue engineered medicinal products[39].

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[38] See EMA, CHMP guidance.

[39] See Article 2(1) of Regulation EC 1394/2007.

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. A biological medicinal product is a product, of which the active substance is a biological substance. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control[40].

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.

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

Contained use. An operation, in which genetically modified organisms are cultured, stored, used, transported, destroyed or disposed of and for which barriers (physical / chemical / biological) are used to limit their contact with the general population and the environment.

Deliberate release. The deliberate release into the environment of genetically modified organisms.

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

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[40] See Annex 1 to Regulation on Registration of Human Medicinal Products – 3.2.1.1(b).

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.

Fermenter. In case of (mammalian) cell lines the term fermenter should be understood as bioreactor.

Founder Animal. An organism that carries a transgene in its germ line and can be used in matings to establish a pure-breeding transgenic line, or one that acts as a breeding stock for transgenic animals.

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

Gene transfer. A process to transfer a gene in cells, involving an expression system contained in a delivery system known as a vector, which can be of viral, as well as non-viral origin. After gene transfer, genetically modified cells are also termed *transduced cells*.

Genetically modified organism (GMO) – means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

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.

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 organism.

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.

Primary cell lot – a pool of primary cells minimally expanded to attain a sufficient number for a limited number of applications**.**

Responsible Person (RP). A person responsible for securing that each batch of (biological) active substance or medicinal product has been manufactured and checked in compliance with the laws in force and in accordance with the specifications and/or requirements of the marketing authorisation[41].

Responsible Person (RP) for blood or tissue establishment. Service Unit Responsible[42].

Scaffold – a support, delivery vehicle or matrix that may provided 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 (SPF). 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.

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

Vector. An agent of transmission, which transmits genetic information from one cell or organism to another, e.g. plasmids, liposomes, viruses.

Viral vector. A vector derived from a virus and modified by means of molecular biology techniques in a way as to retain some, but not all, the parental virus genes; if the genes responsible for virus replication capacity are deleted, the vector is made replication-incompetent.

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.

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41 For Responsible Person see Regulation on Manufacturing Sites for Human Medicinal Products.

42 Article 12 of Regulation on Blood and Blood Products; Article 8, (2) of Regulation on Quality and Safety of Human Tissues and Cells and Related Establishments.

ANNEX 3

MANUFACTURE OF RADIOPHARMACEUTICALS

PRINCIPLE

The manufacture of radiopharmaceuticals should 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 hospitals using Generators and Kits with a marketing authorisation or a national licence, is not covered by this guideline.

Note ii. According to radiation protection regulations it should be ensured that any medical exposure is under the clinical responsibility of a radiation prevention expert (TAEK Radiation Safety Regulation number 23999, dated 24.03.2000. In diagnostic and therapeutic nuclear medicine practices a medical physics expert should be available.

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

Note iv. Transport of radiopharmaceuticals is regulated by the Turkish Atomic Energy Association (TAEK) 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 radioactive isotopes. Particular attention must be paid to the prevention of cross-contamination, to the retention of radionuclide contaminants, and to waste disposal.

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

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

- Radiopharmaceuticals

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

Type of manufacture		Non - GMP *		GMP part II & I (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 GMP Guide, Annex 1.

7. Specifications and quality control testing procedures for the most commonly used radiopharmaceuticals are specified in the European (or other relevant) 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 GMP Guide, Annex 11.

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 Responsible Person 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 additional training adapted to this class of products. .

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

PREMISES AND EQUIPMENT

General

16. Radioactive products 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 GMP Guide, 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 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 GMP Guide, Annex 9. 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 Responsible Person. Where certain test results are not available before use of the product, the Responsible 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 Responsible Person.

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, pre-established 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 Responsible 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 should 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 should 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 Agency, 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 radiolabelling 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.

Responsible person: person recognised by the authority as having the necessary basic scientific and technical background and experience.

ANNEX 4

MANUFACTURE OF MEDICINAL GASES

PRINCIPLE

Gases which fulfill the definition of "human medicinal product" given in the Regulation on Manufacturing Sites for Human Medicinal Products and in the Communiqué on Manufacturing, Filling, Storage and Sales Sites for Medicinal Gases are subject to this guide.

This Annex deals with the manufacture of active substance gases and 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 the Manufacturing Authorization dossier for each product. 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 Manufacturing Authorization 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; 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 the manufacture and distribution of medicinal gases should receive an appropriate GMP training 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 a separate area 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 to avoid the risk of mix-up. Premises should be designated 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 specifications (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 international or national 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 the 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 cylinder is traceable to significant aspects of the relevant filling operations. As appropriate, the following should be entered:

a) the name of the product;

b) batch number;

c) the date and the time of the filling operations;

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 fill at standard conditions;

j) results of appropriate checks to ensure the containers 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 Responsible 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:

a) name of the product;

b) batch number;

c) identification reference for the tank (tanker) in which the batch is certified;

d) date and time of the filling operation;

e) identification of the person(s) carrying out the filling of the tank (tanker);

f) reference to the supplying tanker (tank), reference to the source gas as applicable;

g) relevant details concerning the filling operation;

h) specification of the finished product and results of quality control tests (including reference to the calibration status of the test equipment);

i) details of any problems or unusual events, and signed authorisation for any deviation from filling instructions; and

j) certification statement by the Responsible Person, date and signature.

PRODUCTION

Transfers and deliveries of cryogenic and liquefied gas

19. The transfers of cryogenic or liquefied gases from primary storage, including controls before transfers, should be in accordance with validated procedures designed to avoid any contamination. Transfer lines should be equipped with non-return valves or other suitable alternatives. Flexible connections, and 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 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. 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 get 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 in place to ensure 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 still is valid; and

h) a check to determine that each container is colour-coded as specified (colour-coding of the relevant national / international standards).

31. A batch should be defined for filling operations.

32. Cylinders which have been returned for refilling should be prepared with care in order to minimise risks for contamination in line with the predefined procedures. 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 predefined procedures. 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 tamperevident seal or device (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 or devices.

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 specifications and certified.

40. 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 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. 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.

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

Definition of terms relating to manufacture of medicinal gases, which are not given in the glossary of the current GMP Guide, but which are used in this Annex are given below.

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 is entirely gaseous at all temperatures above -50^0 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
Gas which liquefies at 1.013 bar at temperatures below -150^0 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, which are fastened together interconnected by a manifold, 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 $+20^0$ C or has a vapour pressure exceeding 3 bar at $+ 50^0$ 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 -50^0 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 coming from a possible backflow that remains after the cylinders pre-treatment before filling. The calculation of the maximum theoretical residual impurity is only relevant for compressed gases and supposes that these gases act as perfect gases.

Medicinal gas
Any gas or mixture of gases classified as a medicinal product.

Minimum pressure retention valve
A cylinder valve, which maintains a positive pressure above atmospheric pressure in a gas cylinder after use, in order to prevent internal contamination of the cylinder.

Mobile cryogenic vessel
Mobile thermally insulated container designed to maintain the contents in a liquid state. In the Annex, this term does not include the tankers.

Non-return valve
Valve which permits flow in one direction only.

Purge
To remove the residual gas from a container / system by first pressurising and then venting the gas used for purging to 1.013 bar.

Tank
Static thermally insulated container designed for the storage of liquefied or cryogenic gas. They are also called "Fixed cryogenic vessels".

Tanker
In the context of 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 5

MANUFACTURE OF HERBAL MEDICINAL PRODUCTS

GLOSSARY

1. Herbal Medicinal Product: Herbal substances compounded with one or more of the active substances of a product, or one or more preparations, or one or more such preparations with herbal origin.

2. Herbal Substance: Plants cut or broken into pieces from a whole, plant parts, algae, fungi, non-treated and usually dried or occasionally fresh lichen. Exudates subjected to specific samples are also considered as herbal substances. Herbal substances are identified according to the used plant parts and with their botanic name in the binominal system.

3. Herbal Preparation: Preparations obtained as a result of the processes performed on herbal substances, such as extraction, distillation, expression, decomposition, purification, saturation, fermentation, etc. These include comminuted or powdered herbal products, colouring agents, extracts, essential oils, expressed drinks, and processed exudates.

4. Good Agricultural Practices: Regulation on Good Agricultural Practices issued by Ministry of Food, Agriculture and Livestock.

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 an herbal medicinal product[1] can be a medicinal plant, an herbal substance[2] or an herbal preparation[1]. The herbal substance should 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 Regulation on Good Agricultural Practices or international guidance documents on Good Agricultural and Collection Practice for starting materials of herbal origin. These starting materials should have good agricultural practice certificates.

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

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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 are considered to be equivalent to the terms herbal drug and herbal drug preparation respectively.

Table illustrating the application of Good Practices to the manufacture of herbal medicinal products

Activity	**Good Agricultural and Collection Practice (GACP)**	**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 Notes

* 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 national or international standards of Good Agricultural and Collection Practice for starting materials of herbal origin (GACP) are 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 national or international standards of 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. The Agency 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.

PREMISES

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 crude 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 as to allow free circulation of air.

3. Special attention should be paid to the cleanliness and good 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 verify, where appropriate, whether the suppliers of the herbal substance / preparation are in compliance with Good Agricultural and Collection Practice and – if not – apply appropriate controls in line with Quality Risk Management (QRM).

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 relevant 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 relevant Pharmacopoeia methods or, in absence of 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 relevant 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 temperatures 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 relevant Pharmacopoeia. 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 herbal medicinal products should be determined in accordance with the relevant current national or international guidance on quality and specifications of herbal medicinal products and traditional herbal medicinal products and, where relevant, to specific pharmacopoeial monographs.

ANNEX 6

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 non-representative 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 to GMP, items 6.11 to 6.14. These supplementary guidelines give 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 will be incorrectly identified on its label.

3. This validation should take account of at least the following aspects:

   – 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 arrangements, 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 products 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 the knowledge of 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 7

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.

Note: The manufacture of liquids, creams and ointments must be done in accordance with the GMP described in the GMP Guide and with the other supplementary guidelines, where applicable. The present guidelines only stress points which are specific to this manufacture.

PREMISES AND EQUIPMENT

1. The use of closed systems of 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 product contact parts.

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 sanitization 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 respected.

ANNEX 8

MANUFACTURE OF PRESSURISED METERED DOSE AEROSOL PREPARATIONS FOR INHALATION

PRINCIPLE

Manufacture of pressurised aerosol products for inhalation with metering valves requires some special provisions arising from the particular nature of this pharmaceutical form. It should occur 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.

Note: The manufacture of metered dose aerosols must be done in accordance with the GMP described in the GMP Guide and with the other supplementary guidelines, where applicable. The present guidelines only stress points which are specific to this manufacture.

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 filled 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 and/or at a low temperature. 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 a more complex engineering article than most pharmaceutical components. Specifications, sampling and testing should be appropriate for this situation. 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 provided 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 9

COMPUTERISED SYSTEMS

PRINCIPLE

This annex applies to all forms of computerised systems used as part of a GMP regulated activities. A computerised system is a set of software and hardware components which together fulfil certain functionalities.

The application should be validated; IT infrastructure should be qualified.

Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality, process control or quality assurance. There should be no increase in the overall risk of the process.

GENERAL

1. Risk Management

Risk management should be applied throughout the lifecycle of the computerised system taking into account patient safety, data integrity and product quality. As part of a risk management system, decisions on the extent of validation and data integrity controls should be based on a justified and documented risk assessment of the computerised system.

2. Personnel

There should be close cooperation between all relevant personnel such as Process Owner, System Owner, the Responsible Person 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 the Responsinle Person 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/Customised 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 10

USE OF 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 products 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 *"EMA, 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.

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 non-pharmaceutical materials, provided there is no risk of the former being contaminated by the latter.

Any possibility of contamination of the products by radionuclide from the source must be excluded.

PROCESSING

29. Irradiation containers should be packed in accordance with the specified loading pattern(s) established during validation.

30. During the process, the radiation dose to the irradiation containers should be monitored using validated dosimetry procedures. The relationship between this dose and the dose absorbed by the product inside the container must have been established during process validation and plant commissioning.

31. Radiation indicators should be used as an aid to differentiating irradiated from non-irradiated containers. They should not be used as the sole means of differentiation or as an indication of satisfactory processing.

32. Processing of mixed loads of containers within the irradiation cell should only be done when it is known from commissioning trials or other evidence that the radiation dose received by individual containers remains within the limits specified.

33. When the required radiation dose is by design given during more than one exposure or passage through the plant, this should be with the agreement of the holder of the marketing authorisation and occur within a predetermined time period. Unplanned interruptions during irradiation should be notified to the holder of the marketing authorisation if this extends the irradiation process beyond a previously agreed period.

34. Non-irradiated products must be segregated from irradiated products at all times. Methods or 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 or 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 11

MANUFACTURE OF INVESTIGATIONAL MEDICINAL PRODUCTS

PRINCIPLE

Investigational medicinal products should be produced in accordance with the principles and the detailed guidelines of Good Manufacturing Practice for Medicinal Products. Other guidelines 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, 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

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 the Responsible 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 a manufacturing authorisation. This authorisation, however, shall not be required for reconstitution. 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.

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 means the deliberate disguising of the identity of the product in accordance with the instructions of the sponsor. Unblinding means 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 holder of the authorisation to manufacture/import**.**

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; the investigator

directly responsible for the trials conducted within TUBITAK, DPT or scientific university projects; the trial coordinator for multi-center clinical trials where there are no sponsors for the investigator; and the responsible investigator in singular trials.

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 Responsible Person should ensure that there are systems in place that meet the requirements of GMP and have a broad knowledge of pharmaceutical development and clinical trial processes. Guidance for the Responsible 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.

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 Responsible Person and should therefore be accessible to him/her. Where different manufacturing steps are carried out at different locations under the responsibility of different Responsible Persons, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations.

Manufacturing formulae and processing instructions

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 for 1 year after the expiry date of the investigational medicinal product, and at least for 5 years batch release date.

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. A method should be adopted for investigational medicinal products via labelling to protect and monitor the users, define the product and the trial, and ensure correct use of the investigational medicinal product. 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[1], 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 secondary 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 packaging together with secondary packaging that is intended to remain together, and the secondary packaging carries the particulars listed in paragraph 26, the following information should be included on the label of the primary package (or any sealed dosing device that contains the primary packaging):

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[1] For closed blinded trials, the labelling should include a statement indicating "placebo or [name/identifier] + [strength/potency]".

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, outer packaging should be provided bearing a label with those particulars. The immediate container 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[2].

32. For clinical trials with certain characteristics 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 and accepted by the Agency, it may be performed preferably by a pharmacist or appropriately trained clinical trial monitor(s) under the supervision of the responsible investigator. Where this is not possible, it may be performed at the warehouses carrying out storage activities for investigational medicinal products which are inspected and found appropriate in accordance with "Guidance on the storage and distribution of the investigational products used

[2] E.g. labels for cytotoxic products or for products requiring special storage conditions

for clinical trials" issued by the Agency and GMP principles, on the condition that this activity is limited to changing the expiry date of investigational medicinal product(s). The operation at these warehouses should be performed by appropriately trained clinical trial monitor(s) under the responsibility of the Responsible warehouse pharmacist in accordance with GMP principles, specific and standard operating procedures, relevant national legislations and under contract, if applicable. 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 required information. Verification of the effectiveness of blinding should be performed and recorded.

36. Samples are retained to fulfil 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, labelling, 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.

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 9.

RELEASE OF BATCHES

38. Release of investigational medicinal products (see paragraph 43) should not occur until after the Responsible Person has certified that the relevant requirements have been met. The Responsible Person should take into account the elements listed in paragraph 40 as appropriate.

39. Investigational medicinal products manufactured in Turkey or in other countries should comply with GMP requirements.

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 Responsible Person 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 authorization, in Turkey or in other countries) and its phase of development.

The sponsor should ensure that the elements taken into account by the Responsible Person when certifying the batch are consistent with the required information. See also 44.

41. Where investigational medicinal products are manufactured and packaged at different sites under the supervision of different Responsible Persons, recommendations should be followed as applicable.

42. Packaging or labelling is carried out, in the approved sites in accordance with the legislation and as allowed in this legislation, preferably by a pharmacist or appropriately trained clinical trial monitor(s) under the supervision of the responsible investigator at the investigator site, or at the warehouses conducting storage activities for investigational medicinal products that are inspected and found appropriate by the Agency, under the responsibility of the pharmacist who is the Responsible person for the warehouse, by appropriately trained clinical trial monitor(s). The sponsor is nevertheless responsible for ensuring that the activity is adequately documented and carried out in accordance with the relevant regulations and adequately documented.

SHIPPING

43. Investigational medicinal products should remain under the control of the Sponsor until after completion of a two-step procedure: certification by the Responsible Person; and release following fulfillment of the relevant requirements (commencement of a clinical trial). The Sponsor should ensure that the details set out in the clinical trial application and considered by the Responsible Person are consistent with what is finally accepted by the Agency. 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 Responsible Person and the Sponsor. Both steps should be recorded and retained in the relevant trial files held by or on behalf of 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 s hould 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 Responsible Person should be sought. The product should be

returned to the manufacturer, or another authorised manufacturer for re-labelling, if necessary, and certification by the Responsible 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 Responsible Person and those responsible for the relevant clinical trial in order to assess any potential impact on the trial, product development and on subjects.

RECALLS AND RETURNS

Recalls

49. Procedures for retrieving investigational medicinal products and documenting this retrieval should be agreed by the sponsor, in collaboration with the manufacturer or importer where different. The investigator, the sponsor 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 and the Agency should be informed. These documents should clearly identify, or allow traceability to, the batches and/or patient numbers involved and the actual quantities destroyed.

ANNEX 1. 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[3], 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

[3] For closed blinded trials, the labelling should include a statement indicating "placebo or [name/identifier] + [strength/potency]".

[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.

ANNEX 2. CONTENT OF THE BATCH CERTIFICATE

(1) Names of products/product identifiers as referred to in the clinical trial application.

(2) Sponsor protocol code number.

(3) Strength.

Identifying name and amount per unit dose for the active substance of the investigational medicinal product (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, etc.).

(6) Batch number.

(7) Expiry/retest 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 Qualified Person.

(12) Certification statement.

(13) “I hereby certify that this batch complies with the regulations on clinical trials".

(14) Name of the Qualified Person signing the certificate.

(15) Signature.

(16) Date of signature.

ANNEX 12

MANUFACTURE OF MEDICINAL PRODUCTS DERIVED FROM HUMAN BLOOD OR PLASMA

CONTENTS

GLOSSARY

Blood
Blood means whole blood collected from a single (human) donor and processed either for transfusion or for further manufacturing.

Blood component
A blood component means a therapeutic constituent of blood (red cells, white cells, platelets and plasma) that can be prepared by various methods, using conventional blood bank methodology (e.g. centrifugation, filtration, freezing). This does not include haematopoietic progenitor cells.

Blood establishment
A blood establishment 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. Whilst this definition does not include hospital blood banks, it includes plasma apheresis centers.

Blood products
A blood product 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 national standards and specifications defined for quality systems in blood establishments.

Medicinal products derived from human blood or human plasma
Medicinal products derived from human blood or human plasma 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 (or other relevant) Pharmacopoeia (Ph. Eur.) monograph “Human Plasma for fractionation” (0853).

Plasma Master File (PMF)
A Plasma Master File 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
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.

Responsible Person (RP)
The person responsible for securing that each batch of (biological) active substance or medicinal product has been manufactured and checked in compliance with the laws in force and in accordance with the specifications and/or requirements of the marketing authorization who is referred in the Regulation on Manufacturing Sites for Human Medicinal Products.

Responsible Person (RP) for blood establishment
A person responsible for ensuring that every unit of blood or blood components has been collected and tested, processed, stored and distributed in compliance with the laws in force and may provide the Agency with information on registration procedures.

Contract fractionation program
This is a contract fractionation in a national plant of a fractionator/manufacturer, using starting material from other countries and manufacturing products not intended for the national market.

Note: In the context of this annex, the term Agency refers to Turkish Medicines and Medical Devices Agency and the term Ministry refers to Ministry of Health as a whole.

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 country. The Annex applies also to the starting material (e.g. human plasma) for these products. In line with national legislation the requirements may 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 collection, 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 other countries and for contract fractionation programs for other 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 well as the relevant marketing authorisation. 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. 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 national or international requirements for blood establishments involved in the collection, preparation and testing are to be followed. Collection, preparation and testing must be performed in accordance with an appropriate quality system and for which standards and specifications are defined. Furthermore, the national or international requirements on traceability and serious adverse reactions and serious adverse event notifications from the donor to the recipient should be applied. In addition the monographs of the relevant Pharmacopoeia are to be observed.

2.3 Starting material for the manufacture of medicinal products derived from human blood or plasma imported from other countries and intended for use or distribution within the country must meet the national standards.

2.4 In the case of contract fractionation programs the starting material imported from other countries must comply with the national or equivalent quality and safety requirements for blood components. The activities conducted within the country must fully comply with GMP. Consideration should be given to national standards and specifications relating to a quality system for blood establishments, the traceability requirements and notification of serious adverse reactions and events and the relevant WHO guidelines and recommendations.

2.5 All subsequent steps after collection and testing (e.g. processing (including separation), freezing, storage and transport to the manufacturer) 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 Responsible 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 Responsible Person may, however, not be proportionate given

the presence and responsibility of a Responsible Person of the blood establishment. To address this particular situation and to ensure the legal responsibilities of the Responsible 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 Responsible Person of the fractionation/manufacturing plant (see 3.5) should be involved in drawing up this contract. The Responsible Person should ensure that audits are performed to confirm that the blood establishment complies with the contract.

2.6 Depending on national legislation, 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 in the blood establishment up to delivery of the finished product by the finished product manufacturer. Traceability of each donation up to and including the delivery of plasma to the fractionation plant should be ensured by the blood establishment through accurate identification procedures, record maintenance and an appropriate labelling system according to national or international requirements, and should be maintained during further manufacturing and distribution of final products by the manufacturer.

3.2 Blood or plasma used as source material for the manufacture of medicinal products must be collected and processed by blood establishments and be tested in laboratories which apply quality systems in accordance with national or international standards. Reference is made to documents listed in the addendum. The blood establishments have to be authorised and subject to regular inspections by the competent authority. Contract fractionation programs have to be notified to the Ministry by the manufacturer.

3.3 If plasma is imported from other 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 the competent authority (e.g. following an inspection) of the importing country and by the Responsible Person of the importing fractionation plant. 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 including test laboratory 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 units[1].
- 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 of 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 RP).

4.3 Data needed for full traceability must be stored for at least 30 years.

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.

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[1] Plasma units donated by donors during a defined period (as defined on a national / EU basis) before it is found that a donation from a high-risk donor should have been excluded from processing, e.g. due to a positive test result.

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 serious adverse events and reactions and other relevant information found subsequent to donor acceptance or release of the plasma, e.g. look back information[2] (post-collection information). Where the fractionation plant/manufacturer is located in another country, the information should be forwarded to the manufacturer responsible for release in the country 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 Agency.

4.6 The notification procedure as described in 4.5 also applies when an inspection of a blood establishment by the Ministry 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 Ministry. 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.

The blood establishment and the fractionation plant/manufacturer should inform each other if, following donation:

- It is found that the donor did not meet the relevant donor health criteria;
- A subsequent donation from a donor previously found negative for viral markers is found positive for any of the viral markers;
- It is discovered that testing for viral markers has not been carried out according to agreed procedures;
- The donor has developed an infectious disease caused by an agent potentially transmissible by plasma-derived products (HBV, HCV, HAV and other non-A, non-B, non-C hepatitis viruses, HIV-1 and 2 and other agents in the light of current knowledge);
- The donor develops Creutzfeldt-Jakob disease (CJD or vCJD);
- The recipient of blood or a blood component develops post-transfusion infection which implicates or can be traced back to the donor.

In the event of any of the above, a re-assessment of the batch documentation should always be carried out. The need for withdrawal of the given batch should be carefully considered, taking into account criteria such as the transmissible agent involved, the size of the pool, the time period between donation and seroconversion, the nature of the product and its manufacturing method.

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 PIC/S 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 GMP Guide.

[2] 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.

5.2 Environmental monitoring should be performed regularly, especially during the 'opening' of plasma containers, and during subsequent thawing and pooling processes in accordance with Annex 1 of the GMP Guide.

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 before and 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 "Note for Guidance on Virus Validation Studies: The Design, Contribution and Interpretation of Studies validating the Inactivation and Removal of Viruses" in its current version as adopted by the Committee for Medicinal Products for Human Use (CHMP) and published by the European Medicines Agency.

6. MANUFACTURING

Starting material

6.1 The starting material should comply with the requirements of all relevant monographs of the relevant Pharmacopoeia and of the conditions laid down in the respective marketing authorisation dossier (including the Plasma Master File if applicable). 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 imported for 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*", or other relevant Pharmacopoeia), 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 of the blood establishment (or in case of blood/plasma collection in other 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 Responsible Person. The Responsible 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 if applicable) or, in case of plasma to be used for 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 which take this risk into consideration should be in place.

6.12 Any reprocessing or reworking may only be performed after a quality risk management exercise has been performed and using processing steps as defined in the relevant marketing authorisation.

6.13 A system for clearly segregating/distinguishing between products or intermediates which have undergone a process of virus reduction, from those which have not, should be in place.

6.14 Depending on the outcome of a thorough risk management process (taking into consideration possible differences in epidemiology) production in campaigns including clear segregation and defined validated cleaning procedures should be adopted when plasma/intermediates of different origins is processed at the same plant. The requirement for such measures should be based on Guideline on Epidemiological Data on Blood Transmissible Infections, EMEA/CPMP/BWP/125/04.

6.15 The risk management process should consider whether it is necessary to use dedicated equipment in the case of contract fractionation programs.

6.16 For intermediate products intended to be stored, a shelf-life should be

defined based on stability data.

6.17 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 Pharmacopoeia monographs.

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 Pharmacopoeia monographs, including any specific virus cut-off limits, and with the approved specifications (e.g. Plasma Master File if applicable), 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 Responsible Person and in accordance with the approved marketing authorisation.

8.3. The release of intermediates and final products used in contract fractionation programs should be performed by the Responsible Person on the basis of standards agreed with the contract giver and compliance with GMP standards.

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).

Legislations about Blood and Blood Products:

Additional legislations to this annex are mentioned below, but are not limited to these. It does not cover manufacturing authorisation, marketing authorisation, GMP and other relevant issues and the references made throughout the annex.

Legislation	**Basis/References**
Blood and Blood Products Law, No.5624	-
Regulation on Blood and Blood Products	Blood and Blood Products Law, No.5624
National Guideline on Blood and Blood Products	Blood and Blood Products Law, No.5624 Regulation on Blood and Blood Products EU Directive 2002/98/EC EU Directive 2004/33/EC EU Directive 2005/61/EC EU Directive 2005/62/EC

ANNEX 13

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 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 relevant guidelines on Process Validation (e.g. see EMA Guideline on process validation for finished products - information and data to be provided in regulatory submissions).

5.2.1 A 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 the 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[1], 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 the GMP guide.

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.

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[1] Legacy product is a product developed in the past but still exists on the market.

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 Reponsible 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 GMP guide 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 (e.g. see EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities). 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.

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 the GMP Guide.

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 person 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 Guide to GMP 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.

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.

Worst Case

A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

ANNEX 14

PARAMETRIC RELEASE

1. PRINCIPLE

1.1 The definition of Parametric Release used in this Annex is based on that proposed by the European Organization for Quality: "A system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing process and on the compliance with specific GMP requirements related to Parametric Release."

1.2 Parametric release should comply with the basic requirements of GMP, with applicable annexes and the following guidelines.

2. PARAMETRIC RELEASE

2.1 It is recognised that a comprehensive set of in-process tests and controls may provide greater assurance of the finished product meeting specification than finished product testing.

2.2 Parametric release may be authorised for certain specific parameters as an alternative to routine testing of finished products. Authorisation for parametric release should be given, refused or withdrawn jointly by those responsible for assessing products together with the GMP inspectors.

3. PARAMETRIC RELEASE FOR STERILE PRODUCTS

3.1 This section is only concerned with that part of Parametric Release which deals with the routine release of finished products without carrying out a sterility test. Elimination of the sterility test is only valid on the basis of successful demonstration that predetermined, validated sterilising conditions have been achieved.

3.2 A sterility test only provides an opportunity to detect a major failure of the sterility assurance system due to statistical limitations of the method.

3.3 Parametric release can be authorised if the data demonstrating correct processing of the batch provides sufficient assurance, on its own, that the process designed and validated to ensure the sterility of the product has been delivered.

3.4 At present Parametric release can only be approved for products terminally sterilized in their final container.

3.5 Sterilization methods according to European (or other relevant) Pharmacopoeia requirements using steam, dry heat and ionising radiation may be considered for parametric release.

3.6 It is unlikely that a completely new product would be considered as suitable for Parametric Release because a period of satisfactory sterility test results will form part of the acceptance criteria. There may be cases when a new product is only a minor variation, from the sterility assurance point of view, and existing sterility test data from other products could be considered as relevant.

3.7 A risk analysis of the sterility assurance system focused on an evaluation of releasing non-sterilised products should be performed.

3.8 The manufacturer should have a history of good compliance with GMP.

3.9 The history of non sterility of products and of results of sterility tests carried out on the product in question together with products processed through the same or a similar sterility assurance system should be taken into consideration when evaluating GMP compliance.

3.10 A qualified experienced sterility assurance engineer and a qualified microbiologist should normally be present on the site of production and sterilization.

3.11 The design and original validation of the product should ensure that integrity can be maintained under all relevant conditions.

3.12 The change control system should require review of change by sterility assurance personnel.

3.13 There should be a system to control microbiological contamination in the product before sterilisation.

3.14 There should be no possibility for mix ups between sterilised and non sterilised products. Physical barriers or validated electronic systems may provide such assurance.

3.15 The sterilization records should be checked for compliance to specification by at least two independent systems. These systems may consist of two people or a validated computer system plus a person.

3.16 The following additional items should be confirmed prior to release of each batch of product.

- All planned maintenance and routine checks have been completed in the sterilizer used.
- All repairs and modifications have been approved by the sterility assurance engineer and microbiologist.
- All instrumentation was in calibration.
- The sterilizer had a current validation for the product load processed.

3.17 Once parametric release has been granted, decisions for release or rejection of a batch should be based on the approved specifications. Non-compliance with the specification for parametric release cannot be overruled by a pass of a sterility test.

4. GLOSSARY

Parametric Release
A system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing process and on the compliance with specific GMP requirements related to Parametric Release.

Sterility Assurance System
The sum total of the arrangements made to assure the sterility of products. For terminally sterilized products these typically include the following stages:

a) Product design.

b) Knowledge of and, if possible, control of the microbiological condition of starting materials and process aids (e.g. gases and lubricants).

c) Control of the contamination of the process of manufacture to avoid the ingress of microorganisms and their multiplication in the product. This is usually accomplished by cleaning and sanitization of product contact surfaces, prevention of aerial contamination by handling in clean rooms, use of process control time limits and, if applicable, filtration stages.

d) Prevention of mix up between sterile and non sterile product streams.

e) Maintenance of product integrity.

f) The sterilization process.

g) The totality of the Quality System that contains the Sterility Assurance System e.g. change control, training, written procedures, release checks, planned preventative maintenance, failure mode analysis, prevention of human error, validation calibration, etc.

ANNEX 15

REFERENCE AND RETENTION SAMPLES

1. SCOPE

1.1 This Annex to the Guide to Good Manufacturing Practice for Medicinal Products for Human use ("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 11 to the Guide.

2. PRINCIPLE

2.1 Samples are retained to fulfill 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 analyzed 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 authorization, a labelling/packaging query or a pharmacovigilance report.

2.4 Records of traceability of samples should be maintained and be available for review by the Agency.

3. DURATION OF STORAGE

3.1 Reference and retention samples from each batch of finished product should be retained for at least one year after the expiry date. The reference sample should be contained in its finished primary packaging or in packaging composed of the same material as the primary container in which the product is marketed.

3.2 Samples of starting materials (other than solvents, gases or water used in the manufacturing process) should 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 Agency or maybe of different size approved by the Agency. 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 Agency.

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 conditions should be in accordance with the marketing authorisation (e.g. refrigerated storage where relevant).

6. WRITTEN AGREEMENTS

6.1 Where the marketing authorization holder is not the same legal entity as the site(s) responsible for batch release, 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 Good Manufacturing Practice Guide. 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 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 Responsible 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 and packaging materials used for medicinal products, this is the original site of manufacture of the finished product. For finished products, this is the original site of manufacture.

7.2 Reference samples should be stored as follows:

a) For manufactured products, if the manufacturing site and the release site are the same, reference samples should be stored at the release site.

b) For manufactured products, if the manufacturing site and the release site are different, location for storing the reference samples should be determined with a mutual agreement of the parties.

8. RETENTION SAMPLES – GENERAL POINTS

8.1 A retention sample should represent a batch of finished products as distributed and may need to be examined in order to confirm non-technical attributes for compliance with the marketing authorization or national legislation. The retention samples should preferably be stored at the site where the Responsible Person certifying the finished product batch is located.

8.2 Retention samples should be stored as follows:

a) For manufactured products, if the marketing authorization holder and the release site are the same, retention samples should be stored at the release site.

b) For manufactured products, if the marketing authorization holder and the release site are different, location for storing the retention samples should be determined with a mutual agreement of the parties.

8.3 Retention samples should be stored at the premises of an authorised manufacturer in order to permit ready access by the Agency.

9. REFERENCE AND RETENTION SAMPLES IMPORTED PRODUCTS

9.1 For imported products, the importer should sample the reference sample of sufficient size to permit the carrying out, on, at least, two occasions, of the full analytical controls on each imported batch or of different size approved by the Agency and retain for at least one year after the expiry date. It is the importer's responsibility to store beforementioned samples appropriately to present when required by the Agency.

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 Agency 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 Agency. 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 country in which any unexpired batch has been placed on the market.

ANNEX 16

QUALITY RISK MANAGEMENT

FOREWORD AND SCOPE OF APPLICATION

1. This GMP Annex 16 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.

2. 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.

3. 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 16 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.

4. 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.

5. However, for reasons of coherence and completeness, the ICH Q9 guideline has been transferred completely into GMP Annex 16.

INTRODUCTION

6. *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.

7. 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.

8. 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.

9. 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.

10. 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.

11. 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.

SCOPE

12. 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).

PRINCIPLES OF QUALITY RISK MANAGEMENT

13. Two primary principles of quality risk management are:

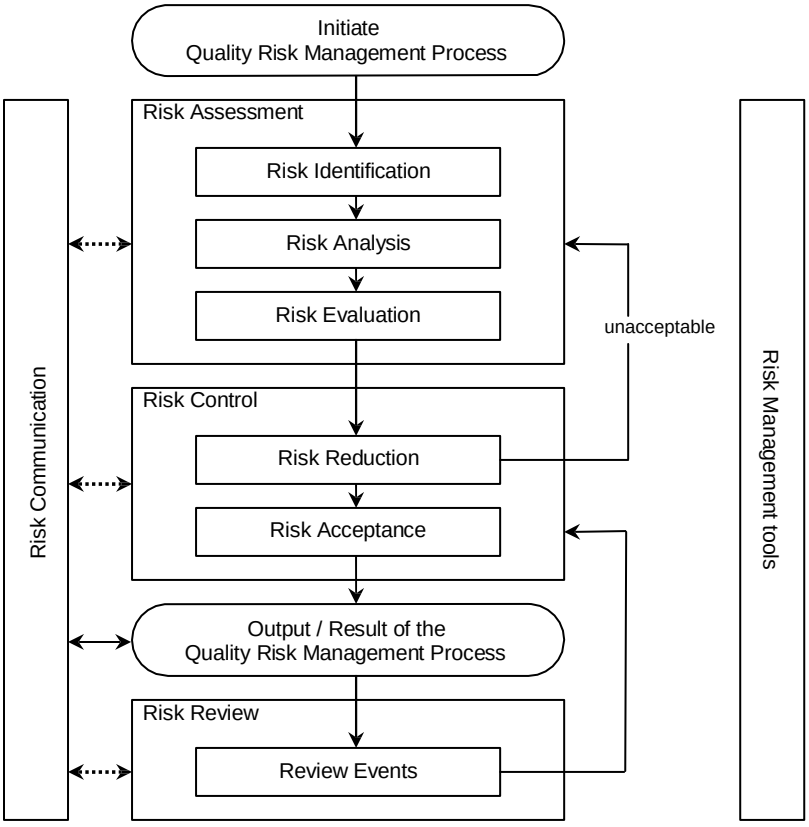
- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient; and
- The level of effort, formality and documentation of the quality risk

management process should be commensurate with the level of risk.

GENERAL QUALITY RISK MANAGEMENT PROCESS

14. 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



15. 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.

Responsibilities

16. 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.

17. 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.

Initiating a Quality Risk Management Process

18. 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

Risk Assessment

19. 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)?

20. ***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.

21. ***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.

22. ***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.

23. 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.

24. 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.

Risk Control

25. *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.

26. 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?

27. ***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.

28. ***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.

Risk Communication

29. ***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 Agency, 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 guidances.

Risk Review

30. Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.

31. 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).

RISK MANAGEMENT METHODOLOGY

32. 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.

33. 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.

34. 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

35. 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.

36. 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.

INTEGRATION OF QUALITY RISK MANAGEMENT INTO INDUSTRY AND REGULATORY OPERATIONS

37. 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.

38. 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.

39. 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.

40. Examples for industry and regulatory operations (see Annex II):

- Quality management

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

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

42. Examples for regulatory operations (see Annex II):

- Inspection and assessment activities

43. While Agency decisions will continue to be taken on a territorial 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.

DEFINITIONS

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

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

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

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

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

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

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

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

Requirements – the explicit or implicit needs or expectations of the patients or their surrogates (e.g. health care professionals, regulators and legislators). In

this document, “requirements” refers not only to statutory, legislative, or regulatory requirements, but also to such needs and expectations.

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

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

Risk analysis – the estimation of the risk associated with the identified hazards

Risk assessment – a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Risk communication – the sharing of information about risk and risk management between the decision maker and other stakeholders

Risk control – actions implementing risk management decisions (ISO Guide 73)

Risk evaluation – the comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk

Risk identification – the systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description

Risk management – the systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating and reviewing risk

Risk reduction – actions taken to lessen the probability of occurrence of harm and the severity of that harm

Risk review – review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk

Severity – a measure of the possible consequences of a hazard

Stakeholder – any individual, group or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry

Trend – a statistical term referring to the direction or rate of change of a variable(s)

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APPENDIX I: RISK MANAGEMENT METHODS AND TOOLS

The purpose of this appendix 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)
- Shewhart Control Charts (see ISO 8258)
- Weighted Moving Average

(ii) Design of Experiments (DOE)

(iii) Histograms

(iv) Pareto Charts

(v) Process Capability Analysis

APPENDIX II: POTENTIAL APPLICATIONS FOR QUALITY RISK MANAGEMENT

This Appendix 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. multi- versus single-purpose, batch versus continuous production)

To determine acceptable (specified) cleaning validation limits

Calibration/preventive maintenance

To set appropriate calibration and maintenance schedules

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

GLOSSARY

Definitions given below apply to the words as used in this Guide. They may have different meanings in other contexts.

Action limit
Established criteria, requiring immediate follow-up and corrective action if exceeded.

Air lock
An enclosed space with two or more doors, and which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when they need to be entered. An air-lock is designed for and used by either people or goods.

Alert limit
Established criteria giving early warning of potential drift from normal conditions which are not necessarily grounds for definitive corrective action but which require follow-up investigation.

Batch (or lot)
A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.

Note: To complete certain stages of manufacture, it may be necessary to divide a batch into a number of subbatches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterised by its intended homogeneity.

For the control of the finished product, a batch of a medicinal products comprises all the units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilisation operation or, in the case of a continuous production process, all the units manufactured in a given period of time.

Batch number (or lot number)
A distinctive combination of numbers and/or letters which specifically identifies a batch.

Biogenerator
A contained system, such as a fermenter, into which biological agents are introduced along with other materials so as to effect their multiplication or their production of other substances by reaction with the other materials. Biogenerators are generally fitted with devices for regulation, control, connection, material addition and material withdrawal.

Biological agents
Microorganisms, including genetically engineered microorganisms, cell cultures and endoparasites, whether pathogenic or not.

Bulk product
Any product which has completed all processing stages up to, but not including, final packaging.

Calibration
The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

Cell bank
Cell bank system: A cell bank system is a system whereby successive batches of a product are manufactured by culture in cells derived from the same master cell bank (fully characterised for identity and absence of contamination). A number of containers from the master cell bank are used to prepare a working cell bank. The cell bank system is validated for a passage level or number of population doublings beyond that achieved during routine production.

Master cell bank: A culture of (fully characterised) cells distributed into containers in a single operation, processed together in such a manner as to ensure uniformity and stored in such a manner as to ensure stability. A master cell bank is usually stored at -70°C or lower.

Working cell bank: A culture of cells derived from the master cell bank and intended for use in the preparation of production cell cultures. The working cell bank is usually stored at -70°C or lower.

Cell culture
The result from the in-vitro growth of cells isolated from multicellular organisms.

Clean area
An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

Note: The different degrees of environmental control are defined in the Supplementary Guidelines for the Manufacture of sterile medicinal products.

Clean/contained area
An area constructed and operated in such a manner that will achieve the aims of both a clean area and a contained area at the same time.

Containment
The action of confining a biological agent or other entity within a defined space.

Primary containment: A system of containment which prevents the escape of a biological agent into the immediate working environment. It involves the use of closed containers or safety biological cabinets along with secure operating procedures.

Secondary containment: A system of containment which prevents the escape of a biological agent into the external environment or into other working areas. It involves the use of rooms with specially designed air handling, the existence of airlocks and/or sterilisers for the exit of materials and secure operating procedures. In many cases it may add to the effectiveness of primary containment.

Contained area
An area constructed and operated in such a manner (and equipped with appropriate air handling and filtration) so as to prevent contamination of the external environment by biological agents from within the area.

Controlled area
An area constructed and operated in such a manner that some attempt is made to control the introduction of potential contamination (an air supply approximating to grade D may be appropriate), and the consequences of accidental release of living organisms. The level of control exercised should reflect the nature of the organism employed in the process. At a minimum, the area should be maintained at a pressure negative to the immediate external environment and allow for the efficient removal of small quantities of airborne contaminants.

Computerised system
A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.

Cross contamination
Contamination of a starting material or of a product with another material or product.

Crude plant (vegetable drug)
Fresh or dried medicinal plant or parts thereof.

Cryogenic vessel
A container designed to contain liquefied gas at extremely low temperature.

Cylinder
A container designed to contain gas at a high pressure.

Exotic organism
A biological agent where either the corresponding disease does not exist in a given country or geographical area, or where the disease is the subject of prophylactic measures or an eradication programme undertaken in the given country or geographical area.

Finished product
A medicinal product which has undergone all stages of production, including packaging in its final container.

Herbal medicinal products
Medicinal products containing, as active ingredients, exclusively plant material and/or vegetable drug preparations.

Infected
Contaminated with extraneous biological agents and therefore capable of spreading infection.

In-process control
Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specification. The control of the environment or equipment may also be regarded as a part of in- process control.

Intermediate product
Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

Liquifiable gases
Those which, at the normal filling temperature and pressure, remain as a liquid in the cylinder.

Manifold
Equipment or apparatus designed to enable one or more gas containers to be filled simultaneously from the same source.

Manufacture
All operations of purchase of materials and products, Production, Quality Control, release, storage, distribution of medicinal products and the related controls.

Manufacturer
Holder of a manufacturing authorisation.

Media fill
Method of evaluating an aseptic process using a microbial growth medium. (Media fills are synonymous to simulated product fills, broth trials, broth fills etc.).

Medicinal plant
Plant the whole or part of which is used for pharmaceutical purpose.

Medicinal products
Any medicine or similar product intended for human use, which is subject to control under health legislation in the manufacturing or importing State.

Packaging
All operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product.

Note: Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not finally packaged, primary containers.

Packaging material
Any material employed in the packaging of a medicinal product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Procedures
Description of the operations to be carried out, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of a medicinal product.

Production
All operations involved in the preparation of a medicinal product, from receipt of materials, through processing and packaging, to its completion as a finished product.

Qualification
Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification.

Quality control
See Chapter 1.

Quarantine
The status of starting or packaging materials, intermediate, bulk or finished products isolated physically or by other effective means whilst awaiting a decision on their release or refusal.

Radiopharmaceutical
"Radiopharmaceutical" means any medicinal products which, when ready for use, contain one or more radionuclides (radioactive isotopes) included for a pharmaceutical purpose.

Reconciliation
A comparison, making due allowance for normal variation, between the amount of product or materials theoretically and actually produced or used.

Record
See Chapter 4.

Recovery
The introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture.

Reprocessing
The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.

Responsible person
Person recognised by the authority as having the necessary basic scientific and technical background and experience.

Return
Sending back to the manufacturer or distributor of a medicinal products which may or may not present a quality defect.

Seed lot
Seed lot system: A seed lot system is a system according to which successive batches of a product are derived from the same master seed lot at a given passage level. For routine production, a working seed lot is prepared from the master seed lot. The final product is derived from the working seed lot and has not undergone more passages from the master seed lot than the vaccine shown in clinical studies to be satisfactory with respect to safety and efficacy. The origin and the passage history of the master seed lot and the working seed lot are recorded.

Master seed lot: A culture of a micro-organism distributed from a single bulk into containers in a single operation in such a manner as to ensure uniformity, to prevent contamination and to ensure stability. A master seed lot in liquid form is usually stored at or below -70°C. A freeze-dried master seed lot is stored at a temperature known to ensure stability.

Working seed lot: A culture of a micro-organism derived from the master seed lot and intended for use in production. Working seed lots are distributed into containers and stored as described above for master seed lots.

Specification
See Chapter 4.

Starting material
Any substance used in the production of medicinal products, but excluding packaging materials.

Sterility
Sterility is the absence of living organisms. The conditions of the sterility tests are given in the European (or other relevant) Pharmacopoeia.*

Validation
Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

* The procedures and precautions employed should be such as to give a theoretical level of not more than one living micro-organism in 10^6 units in the final product.