

MEDICINES CONTROL COUNCIL



GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINES IN SOUTH AFRICA

This document has been prepared to serve as a guidance document on the requirements for Good Manufacturing Practice applicable to the manufacturing of medicines. It is not intended as an exclusive approach. Council reserves the right to request for any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of data accompanying applications for registration of medicines. Alternative approaches may be used but these must be scientifically and technically justified. The MCC is committed to ensure that all medicines gaining market approval will be of the required quality, safety and efficacy.

This Guide is based entirely on the "Guide to Good Manufacturing Practice for Medicinal Products", version PE 009-2 dated 1 July 2004 published by the Pharmaceutical Inspection Cooperation Scheme (PIC/S). The modifications to that Guide and its adoption as the South African Guide to Good Manufacturing Practice is done so with the expressed permission of the PIC/S.

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REGISTRAR OF MEDICINES
MS M HELA

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* The ICH GMP Guide on APIs has been provisionally adopted by the European Commission as Annex 18 to the EC GMP Guide while the same document has been adopted as a stand-alone document by the PIC/S Committee (PE 007).

INTRODUCTION

GENERAL

In order to further facilitate the removal of barriers to trade in medicinal products, to promote uniformity in licensing decisions and to ensure the maintaining of high standards of quality assurance in the development, manufacture and control of medicinal products the following Guide to Good Manufacturing Practice for Medicinal Products and its Annexes has been adopted.

The standards set out herein, apply to medicines and similar products intended for human use. It is recommended, however, that the same kind of attention be given to the manufacture of veterinary products. Administrative measures of national health authorities should be directed towards the application of these standards in practice, and any new or amended national regulations for good manufacturing practice should at least meet their level. These standards are also intended to serve manufacturers as a basis for the elaboration of specific rules adapted to their individual needs.

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In addition to the general matters of Good Manufacturing Practice outlined in the chapters of this guide, supplementary guidelines such as the Technical Series of the World Health Organisation can be used to clarify and support specific areas of activity.

The standards set out herein, apply to medicines and similar products intended for human and veterinary use.

It is recognised that there are acceptable methods, other than those described in this Guide, which are capable of achieving the principles of the Guide. This Guide is not intended to place any restraint upon the development of new concepts or new technologies, which have been validated and provide a level of Quality Assurance at least equivalent to those set out in this Guide.

The Guide is divided into two parts and a number of annexes, which are common to both parts. Part I covers GMP principles for the manufacture of medicinal products. Part II covers GMP for active substances used as starting materials. The annexes provide detail on specific areas of activity. For some manufacturing processes, different annexes will apply simultaneously (e.g. annex on sterile preparations and on radiopharmaceuticals and/or on biological medicinal products). A glossary of some terms used in the Guide has been incorporated after the annexes.

HISTORY

Part I of the PIC/S GMP Guide

Originally, the PIC/S GMP Guide derives from the WHO GMP Guide and was further developed in order to comply with stringent manufacturing and health requirements in PIC/S countries, to cover new areas (e.g. biologicals, radiopharmaceuticals, etc.) and to adapt to scientific and industrial technology (e.g. biotech, parametric release etc.). The aim of such improvements was to ensure that high quality medicines were produced in line with the PIC Convention and then the Scheme.

In the late 1980s / early 1990s the PIC/S GMP Guide was taken over by the EU and further developed in close co-operation with PIC/S. Since that time, the EU and the PIC/S GMP Guides have been developed in parallel and whenever a change has been made to one, the other has been amended so that both Guides are practically identical.

There are, however, some differences between the two Guides. These differences are the following:

- the definition of Pharmaceutical Product (referred to as "Medicinal Product" in this Guide) which is found in Article 1 of the Pharmaceutical Inspection Convention has been retained;
- references to the EU Directives have been deleted;
- the expression "authorised person" (see Glossary) is used in the PIC/S Guide, while the expression "Qualified Person" is used in the EU Guide;

- since all the Contracting States to the PIC Convention or Participating Authorities under the PIC Scheme are not parties to the European Pharmacopoeia Convention, the mention of "European Pharmacopoeia" in the Guide has been amended to read "European or other relevant Pharmacopoeia".

As the Medicines Control Council of South Africa accepts the European, British or United States Pharmacopoeiae "*or other relevant Pharmacopoeia*" has been further amended accordingly.

Part II of the PIC/S GMP Guide

On 22 May 2001, the PIC/S Committee adopted the "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients" (ICH Q7A) developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). It is recalled that the first draft of this GMP Guide for APIs was elaborated by PIC/S, before it was transferred to ICH. At its Düsseldorf meeting on 29-30 May 2006, the PIC/S Committee decided to make it Part II of the current Guide.

CHAPTER 1

QUALITY MANAGEMENT

1.1 PRINCIPLE

- 1.1.1 The holder of a manufacturing licence must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the medicine registration and do not place patients at risk due to inadequate safety, quality or efficacy.
- 1.1.2 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.
- 1.1.3 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.
- 1.1.4 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.
- 1.1.5 There are additional legal responsibilities for the holder of the medicine registration and for the authorised person(s).
- 1.1.6 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.

1.2 QUALITY ASSURANCE

- 1.2.1 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.
- 1.2.2 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 an authorised person has certified that each production batch has been produced and controlled in accordance with the requirements of the medicine registration 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.

1.3 GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS (GMP)

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

1.3.2 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.

1.4 QUALITY CONTROL

1.4.1 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.

1.4.2 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;

1.4 Quality Control continued

- (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 medicine registration, 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 an authorised person that it is in accordance with the requirements of the medicine registration;
- (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.

1.5 PRODUCT QUALITY REVIEW

- 1.5.1 Regular periodic or rolling quality reviews of all registered 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.
- 1.5.2 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 the medicine registration variations/amendments 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 medicine registrations and variations/amendments to medicine registrations, a review of post-marketing commitments.
 - (xi) The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc.
 - (xii) A review of any contractual arrangements as defined in Chapter 7 to ensure that they are up to date.

1.5 Product Quality Review continued

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

1.6 QUALITY RISK MANAGEMENT

- 1.6.1 Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product.
- 1.6.2 It can be applied both proactively and retrospectively.
- 1.6.3 The quality risk management system should ensure that:
- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient
 - the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk

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

CHAPTER 2

PERSONNEL

2.1 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.

2.2 GENERAL

2.2.1 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.

2.2.2 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.

2.3 KEY PERSONNEL

2.3.1 Key Personnel include 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 authorised person(s) designated for the purpose. Normally key posts should be occupied by full-time personnel.

The heads of Production and Quality Control must be independent from each other.

In large organisations it may be necessary to delegate some of the functions listed in 2.3.2, 2.3.3 and 2.3.4 .

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

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

2.3.3 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;

Key Personnel – Head of Quality Control continued

- (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.

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

- the authorization of written procedures and other documents, including amendments;
- the monitoring and control of the manufacturing environment;
- plant hygiene / cleanliness;
- 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 / protection of products and materials against spoilage and deterioration;
- 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.

2.4 TRAINING

2.4.1 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.

2.4.2 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.

2.4.3 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.

2.4.4 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.

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

2.5 PERSONAL HYGIENE

- 2.5.1 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.
- 2.5.2 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.
- 2.5.3 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.
- 2.5.4 Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.
- 2.5.5 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.
- 2.5.6 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.
- 2.5.7 Personnel should be instructed to use the hand-washing facilities.
- 2.5.8 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

3.1 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.

3.2 PREMISES**3.2.1 General**

- (i) 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.
- (ii) 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.
- (iii) 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.
- (iv) Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.
- (v) Steps should be taken in order to prevent the entry of unauthorised people.
- (vi) Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.

3.2.2 Production Area

- (i) 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.
- (ii) 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.
- (iii) 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.

3.2.2 Production Area continued

- (iv) 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.
- (v) 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.
- (vi) 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.
- (vii) 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.
- (viii) Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.
- (ix) 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.
- (x) Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.
- (xi) Production areas should be well lit, particularly where visual on-line controls are carried out.
- (xii) In-process controls may be carried out within the production area provided they do not carry any risk for the production.

3.2.3 Storage Areas

- (i) 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.
- (ii) 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.
- (iii) 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.
- (iv) Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorised personnel. Any system replacing the physical quarantine should give equivalent security.
- (v) 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.
- (vi) Segregated areas should be provided for the storage of rejected, recalled or returned materials or products.
- (vii) Highly active materials or products should be stored in safe and secure areas.
- (viii) 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.

3.2.4 Quality Control Areas

- (i) 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.
- (ii) 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.
- (iii) Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc.
- (iv) Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

3.2.5 Ancillary Areas

- (i) Rest and refreshment rooms should be separate from other areas.
- (ii) 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.
- (iii) 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.
- (iv) Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

3.3 EQUIPMENT

- 3.3.1 Manufacturing equipment should be designed, located and maintained to suit its intended purpose.
- 3.3.2 Repair and maintenance operations should not present any hazard to the quality of the products.
- 3.3.3 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.
- 3.3.4 Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.
- 3.3.5 Equipment should be installed in such a way as to prevent any risk of error or of contamination.
- 3.3.6 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.
- 3.3.7 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.
- 3.3.8 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.
- 3.3.9 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.
- 3.3.10 Distilled, deionized and, where appropriate, other water pipes should be sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.
- 3.3.11 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labelled as defective.

CHAPTER 4

DOCUMENTATION

4.1 PRINCIPLE

Good documentation constitutes an essential part of the quality assurance system.

Clearly written documentation prevents errors from spoken communication and permits tracing of batch history.

Specifications, Manufacturing formulations and instructions, procedures, and records must be free from errors and available in writing.

The legibility of documents is of paramount importance.

4.2 GENERAL

4.2.1 *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.

4.2.2 *Manufacturing Formulations, Processing and Packaging Instructions* state all the starting materials used and lay down all processing and packaging operations.

4.2.3 *Procedures* give directions for performing certain operations e.g. cleaning, clothing, environmental control, sampling, testing, equipment operations.

4.2.4 *Records* provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent for the quality of the final product.

4.2.5 Documents should be designed, prepared, reviewed and distributed with care.

They should comply with the relevant parts of the manufacturing and medicine registration dossiers.

4.2.6 Documents should be approved, signed and dated by appropriate and authorised persons.

4.2.7 Documents should have unambiguous contents; title, nature and purpose should be clearly stated.

They should be laid out in an orderly fashion and be easy to check.

Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

4.2.8 Documents 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.

4.2.9 Documents should not be hand-written; although, where documents require the entry of data, these entries may be made in clear, legible, indelible handwriting.

Sufficient space should be provided for such entries.

4.2.10 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.

4.2.11 The 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.

4.2.12 They should be retained for at least one year after the expiry date of the finished product. Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked.

If documentation is handled by electronic data processing methods, only authorised persons should be able to enter or modify data in the computer and there should be a record of changes and deletions; access should be restricted by passwords or other means and the result of entry of critical data should be independently checked.

4.2 *General continued*

Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper or other means. It is particularly important that the data are readily available throughout the period of retention.

4.3 DOCUMENTS REQUIRED

4.3.1 Specifications

There should be appropriately authorised and dated specifications for starting and packaging materials, and finished products; where appropriate, they should be also available for intermediate or bulk products.

4.3.2 Specifications for starting and packaging materials

Specifications for starting and primary or printed packaging materials should include, 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 possible, the original producer of the products;
 - a specimen of printed materials;
- b) directions for sampling and testing or reference to procedures;
- c) qualitative and quantitative requirements with acceptance limits;
- d) storage conditions and precautions;
- e) the maximum period of storage before re-examination.

4.3.3 Specifications for intermediate and bulk products

Specifications for intermediate and bulk products should be available if these are purchased or dispatched, or if data obtained from intermediate products are used for the evaluation of the finished product. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

4.3.4 Specifications for finished products

Specifications for finished products should include:

- a) the designated name of the product and the code reference where applicable;
- b) the formulation or a reference to;
- c) a description of the pharmaceutical form and package details;
- d) directions for sampling and testing or a reference to procedures;
- 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.

4.4 MANUFACTURING FORMULATIONS AND PROCESSING INSTRUCTIONS

Formally authorised Manufacturing Formulations and Processing Instructions should exist for each product and batch size to be manufactured. They are often combined in one document.

4.4.1 The Manufacturing Formulation 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;

4.4.1 The Manufacturing Formulation continued

- c) a list of all starting materials to be used, with the amount of each, described using the designated name and a reference which is unique to that material; 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.

4.4.2 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) detailed stepwise processing instructions (e.g. checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures);
- d) the instructions for any in-process controls with their limits;
- e) where necessary, the requirements for bulk storage of the products; including the container, labelling and special storage conditions where applicable;
- f) any special precautions to be observed.

4.5 PACKAGING INSTRUCTIONS

There should be formally authorised Packaging Instructions for each product for pack size and type. These should normally include, or have a reference to, the following:

- a) name of the 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 for a standard batch size, 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) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
- g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
- h) details of in-process controls with instructions for sampling and acceptance limits.

4.6 BATCH PROCESSING RECORDS

A Batch Processing Record should be kept for each batch processed.

It should be based on the relevant parts of the currently approved Manufacturing Formulation and Processing Instructions.

The method of preparation of such records should be designed to avoid transcription errors.

The record should carry the number of the batch being manufactured.

Before any processing begins, there should be recorded 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.

4.6 *Batch Processing Records continued*

During processing, the following information should be recorded at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person responsible for the processing operations:

- a) the name of the product;
- b) dates and times of commencement, of significant intermediate stages and of completion of production;
- c) name of the person responsible for each stage of production;
- d) initials of the operator of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g. weighing);
- e) 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);
- f) any relevant processing operation or event and major equipment used;
- g) a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
- h) the amount of product yield obtained at different and pertinent stages of manufacture;
- i) notes on special problems including details, with signed authorization for any deviation from the Manufacturing Formulation and Processing Instructions.

4.7 **BATCH PACKAGING RECORDS**

4.7.1 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 and the method of preparation of such records should be designed to avoid transcription errors.

The record should carry the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained.

4.7.2 Before any packaging operation begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use.

4.7.3 The following information should be entered at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person(s) responsible for the packaging operations:

- a) the name of the product;
- b) the date(s) and times of the packaging operations;
- c) the name of the responsible person carrying out the packaging operation;
- d) the initials of the operators of the different significant steps;
- e) records of checks for identity and conformity with the Packaging Instructions including the results of in-process controls;
- f) details of the packaging operations carried out, including references to equipment and the packaging lines used;
- g) whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any additional overprinting;
- h) notes on any special problems or unusual events including details with signed authorization for any deviation from the Manufacturing Formulation and Processing Instructions;
- i) 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.

4.8 PROCEDURES AND RECORDS

4.8.1 Receipt

There should be written procedures and records for the receipt of each delivery of each starting and primary and printed packaging material.

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, if possible, 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 (e.g. state of the containers).

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

4.8.2 Sampling

There should be written procedures for sampling, which include the person(s) authorised to take samples, 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 (see Chapter 6, Item 6.5.3).

4.8.3 Testing

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 (see Chapter 6, Item 6.6.3).

4.8.4 Other

- (i) Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by the authorised person(s) designated for the purpose.
- (ii) Records should be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary (see Chapter 8).
- (iii) There should be written procedures and the associated records of actions taken or conclusions reached, where appropriate, for:
 - validation;
 - equipment assembly and calibration;
 - maintenance, cleaning and sanitization;
 - personnel matters including training, clothing, hygiene;
 - environmental monitoring;
 - pest control;
 - complaints;
 - recalls;
 - returns.
- (iv) Clear operating procedures should be available for major items of manufacturing and test equipment.

4.8 Procedures and records – Other continued

- (v) Log books should be kept for major or critical equipment recording, as appropriate, any validations, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.
- (vi) Log books should also record in chronological order the use of major or critical equipment and the areas where the products have been processed.

CHAPTER 5

PRODUCTION

5.1 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 medicine registrations.

5.2 GENERAL

- 5.2.1 Production should be performed and supervised by competent people.
- 5.2.2 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.
- 5.2.3 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.
- 5.2.4 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.
- 5.2.5 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.
- 5.2.6 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.
- 5.2.7 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.
- 5.2.8 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.
- 5.2.9 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.
- 5.2.10 At every stage of processing, products and materials should be protected from microbial and other contamination.
- 5.2.11 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.
- 5.2.12 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.
- 5.2.13 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,).
- 5.2.14 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.
- 5.2.15 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.
- 5.2.16 Access to production premises should be restricted to authorised personnel.
- 5.2.17 Normally, the production of non-medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.

5.3 PREVENTION OF CROSS-CONTAMINATION IN PRODUCTION

- 5.3.1 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.

- 5.3.2 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.

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

5.4 VALIDATION

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

- 5.4.2 When any new manufacturing formulation 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.

- 5.4.3 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.

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

5.5 STARTING MATERIALS

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

- 5.5.2 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.

5.5 Starting Materials continued

- 5.5.3 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.
- 5.5.4 If one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing and release.
- 5.5.5 Starting materials in the storage area should be appropriately labelled (see Chapter 5, Item 5.2.15). Labels should bear at least the following information:
- a) the designated name of the product and the internal code reference where applicable;
 - b) a batch number given at receipt;
 - c) where appropriate, the status of the contents (e.g. in quarantine, on test, released, rejected);
 - d) 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.
- 5.5.6 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 6.5.3).
- 5.5.7 Only starting materials which have been released by the Quality Control Department and which are within their shelf-life should be used.
- 5.5.8 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.
- 5.5.9 Each dispensed material and its weight or volume should be independently checked and the check recorded.
- 5.5.10 Materials dispensed for each batch should be kept together and conspicuously labelled as such.

5.6 PROCESSING OPERATIONS - INTERMEDIATE AND BULK PRODUCTS

- 5.6.1 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.
- 5.6.2 Intermediate and bulk products should be kept under appropriate conditions.
- 5.6.3 Critical processes should be validated (see "VALIDATION" in this Chapter).
- 5.6.4 Any necessary in-process controls and environmental controls should be carried out and recorded.
- 5.6.5 Any significant deviation from the expected yield should be recorded and investigated.

5.7 PACKAGING MATERIALS

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

5.8 PACKAGING OPERATIONS

- 5.8.1 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.
- 5.8.2 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.
- 5.8.3 The name and batch number of the product being handled should be displayed at each packaging station or line.
- 5.8.4 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.
- 5.8.5 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.
- 5.8.6 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.
- 5.8.7 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.
- 5.8.8 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.
- 5.8.9 Checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.
- 5.8.10 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.
- 5.8.11 On-line control of the product during packaging should include at least checking the following:
- general appearance of the packages;
 - whether the packages are complete;
 - whether the correct products and packaging materials are used;
 - whether any over-printing is correct;
 - correct functioning of line monitors.
- Samples taken away from the packaging line should not be returned.
- 5.8.12 Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation and approval by authorised personnel. Detailed record should be kept of this operation.
- 5.8.13 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.
- 5.8.14 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.

5.9 FINISHED PRODUCTS

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

5.10 REJECTED, RECOVERED AND RETURNED MATERIALS

- 5.10.1 Rejected materials and products should be clearly marked as such and stored separately in restricted areas.
They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorised personnel.
- 5.10.2 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.
- 5.10.3 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.
- 5.10.4 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.
- 5.10.5 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 reprocessing to recover active ingredients may be possible.
Any action taken should be appropriately recorded.

CHAPTER 6**QUALITY CONTROL****6.1 PRINCIPLE**

Quality Control is concerned with sampling, specifications and testing as well as the organisation, documentation and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory.

Quality Control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product.

The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control (see also Chapter 1).

6.2 GENERAL**6.2.1** Each holder of a medicine registration 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.

6.2.2 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.

6.2.3 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.**6.2.4** Quality Control personnel should have access to production areas for sampling and investigation as appropriate.**6.3 GOOD QUALITY CONTROL LABORATORY PRACTICE****6.3.1** Control Laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3.**6.3.2** 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.

6.4 DOCUMENTATION

- 6.4.1 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.
- 6.4.2 Any Quality Control documentation relating to a batch record should be retained for one year after the expiry date of the batch.
- 6.4.3 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.
- 6.4.4 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.

6.5 SAMPLING

- 6.5.1 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.
- 6.5.2 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).
- 6.5.3 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.
- 6.5.4 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 a full re-examination.

6.6 TESTING

- 6.6.1 Analytical methods should be validated. All testing operations described in the medicine registration should be carried out according to the approved methods.
- 6.6.2 The results obtained should be recorded and checked to make sure that they are consistent with each other. Any calculations should be critically examined.
- 6.6.3 The tests performed should be recorded and the records should include at least the following data:
- name of the material or product and, where applicable, dosage form;
 - batch number and, where appropriate, the manufacturer and/or supplier;
 - references to the relevant specifications and testing procedures;
 - test results, including observations and calculations, and reference to any certificates of analysis;
 - dates of testing;
 - initials of the persons who performed the testing;
 - initials of the persons who verified the testing and the calculations, where appropriate;
 - a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.
- 6.6.4 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.
- 6.6.5 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.
- 6.6.6 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.
- 6.6.7 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.
- 6.6.8 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.

6.7 ON-GOING STABILITY PROGRAMME

- 6.7.1 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.
- 6.7.2 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.

6.7 On-going Stability Programme - continued

- 6.7.3 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.
- 6.7.4 The on-going stability programme should be described in a written protocol following the general rules of Chapter 4 and results formalised as a report. The equipment used for the on-going stability programme (stability chambers among others) should be qualified and maintained following the general rules of Chapter 3 and annex 15.
- 6.7.5 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.
- 6.7.6 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).
- 6.7.7 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.
- 6.7.8 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.
- 6.7.9 Results of on-going stability studies should be made available to key personnel and, in particular, to the Authorised Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned. Results of on-going stability studies should be available at the site of manufacture for review by the competent authority.
- 6.7.10 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with chapter 8 of the GMP Guide and in consultation with the relevant competent authorities.
- 6.7.11 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

7.1 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 authorized person releasing each batch of product for sale exercises his full responsibility.

7.2 GENERAL

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

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

7.3 THE CONTRACT GIVER

7.3.1 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.

7.3.2 The Contract Giver should provide the Contract Acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the medicine registration 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.

7.3.3 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 an authorised person.

7.4 THE CONTRACT ACCEPTOR

7.4.1 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 licence and is specified in the registration dossier.

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

7.4.3 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.

7.4.4 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.

7.5 THE CONTRACT

- 7.5.1 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 medicine registration and agreed by both parties.
- 7.5.2 The contract should specify the way in which the authorised person releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of the medicine registration.
- 7.5.3 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.
- 7.5.4 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.
- 7.5.5 The contract should permit the Contract Giver to visit the facilities of the Contract Acceptor.
- 7.5.6 In case of contract analysis, the Contract Acceptor should understand that he is subject to inspection by the Medicines Control Council.

CHAPTER 8

COMPLAINTS AND PRODUCT RECALL

8.1 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.

8.2 COMPLAINTS

8.2.1 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 authorised person, the latter should be made aware of any complaint, investigation or recall.

8.2.2 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.

8.2.3 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.

8.2.4 If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches should be checked in order to determine whether they are also affected.

In particular, other batches which may contain reworks of the defective batch should be investigated.

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

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

8.2.7 The Medicines Control Council should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, or any other serious quality problems with a product.

8.3 RECALLS

8.3.1 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 authorised person, the latter should be made aware of any recall operation.

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

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

8.3.4 The Medicines Control Council should be informed promptly if products are intended to be recalled because they are, or are suspected of, being defective.

8.3.5 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.

8.3 Recalls continued

- 8.3.6 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.
- 8.3.7 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.
- 8.3.8 The effectiveness of the arrangements for recalls should be evaluated from time to time.

CHAPTER 9

SELF-INSPECTION

9.1 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.

9.1.1 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.

9.1.2 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.

9.1.3 All self-inspections should be recorded.

Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures.

Statements on the actions subsequently taken should also be recorded.

ANNEX 1

MANUFACTURE OF STERILE MEDICINAL PRODUCTS

1.1 PRINCIPLE

The manufacture of sterile products is subject to special requirements in order to minimise risks of microbiological contamination, and of particulate and pyrogens 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 Annex 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.

1.2 GENERAL

1.2.1 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.

1.2.2 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.

1.2.3 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.

1.2 GENERAL continued

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

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

The airborne particulate classification for these grades is given in the following table.

	At rest (b)		In operation (b)	
Grade	Maximum permitted number of particles/m ³ equal to or above (a)			
	0,5 µm (d)	5 µm	5 µm (d)	5 µm
A	3 500	1 (e)	3 500	1 (e)
B (c)	3 500	1 (e)	350 000	2 000
C (c)	350 000	2 000	3 500 000	20 000
D (c)	3 500 000	20 000	not defined (f)	not defined (f)

- Notes: (a) Particle measurement based on the use of a discrete airborne particle counter to measure the concentration of particles at designated sizes equal to or greater than the threshold stated. A continuous measurement system should be used for monitoring the concentration of particles in the grade A zone, and is recommended for the surrounding grade B areas. For routine testing the total sample volume should not be less than 1 m³ for grade A and B areas and preferably also in grade C areas.
- (b) The particulate conditions 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.
The particulate conditions for grade A "in operation" given in the table should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment.
It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.
- (c) In order to reach the B, C and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate terminal filters such as HEPA for grades A, B and C.
- (d) The guidance given for the maximum permitted number of particles in the "at rest" and "in operation" conditions correspond approximately to the cleanliness classes in the EN/ISO 14644-1 at a particle size of 0,5 µm.
- (e) These areas are expected to be completely free from particles of size greater than 5 µm. As it is impossible to demonstrate the absence of particles with any statistical significance, the limits are set to 1 particle / m³. During the clean room qualification it should be shown that the areas can be maintained within the defined limits.
- (f) The requirements and limits will depend on the nature of the operations carried out.

1.2 GENERAL continued

Examples of operations to be carried out in the various grades are given in the table below (see also items 1.5 & 1.6):

Grade	Examples of operations for terminally sterilised products (see 1.5)
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Grade	Examples of operations for aseptic preparations (see 1.6)
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

1.2.4 The areas should be monitored during operation in order to control the particulate cleanliness of the various grades.

1.2.5 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.

Recommended limits for microbiological monitoring of clean areas during operation:

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

Notes: (a) These are average values.

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

1.2.6 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.

1.3 ISOLATOR TECHNOLOGY

- 1.3.1 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.

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.

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 be at least grade D.

- 1.3.2 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, sanitation of the isolator, the transfer process and isolator integrity.

- 1.3.3 Monitoring should be carried out routinely and include frequent leak testing of the isolator and glove/sleeve system.

1.4 BLOW/FILL/SEAL TECHNOLOGY

- 1.4.1 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 for terminal sterilisation should be installed in at least a grade D environment.

- 1.4.2 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.

1.5 TERMINALLY STERILISED PRODUCTS

- 1.5.1 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 there is unusual risk to the product because 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, preparation should be done in a grade C environment.

1.5 TERMINALLY STERILISED PRODUCTS continued

- 1.5.2 Filling of products for terminal sterilisation should be done in at least a grade C environment.
- 1.5.3 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 done in a grade C environment before terminal sterilisation.

1.6 ASEPTIC PREPARATION

- 1.6.1 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.
- 1.6.2 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.
- 1.6.3 Handling and filling of aseptically prepared products should be done in a grade A environment with a grade B background.
- 1.6.4 Transfer of partially closed containers, as used in freeze drying, should, prior to the completion of stoppering, be done either in a grade A environment with grade B background or in sealed transfer trays in a grade B environment.
- 1.6.5 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.

1.7 PERSONNEL

- 1.7.1 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.
- 1.7.2 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, including 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.
- 1.7.3 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.
- 1.7.4 High standards of personnel 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.
- 1.7.5 Changing and washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas.
- 1.7.6 Wristwatches, make-up and jewellery should not be worn in clean areas.
- 1.7.7 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.

1.7 PERSONNEL continued

1.7.8 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.
Trousers-bottoms 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.

- 1.7.9 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 at every working session.
- 1.7.10 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.

1.8 PREMISES

- 1.8.1 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.
- 1.8.2 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.
- 1.8.3 False ceilings should be sealed to prevent contamination from the space above them.
- 1.8.4 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.
- 1.8.5 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 back-flow.

1.8 PREMISES continued

- 1.8.6 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.
- 1.8.7 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.
- 1.8.8 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 Pascal (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.
- 1.8.9 It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle-generating person, operation or machine to a zone of higher product risk.
- 1.8.10 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.

1.9 EQUIPMENT

- 1.9.1 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).
- 1.9.2 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 after complete reassembly wherever possible.
- 1.9.3 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.
- 1.9.4 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.
- 1.9.5 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.

1.10 SANITATION

- 1.10.1 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.
- 1.10.2 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.
- 1.10.3 Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places.

1.11 PROCESSING

- 1.11.1 Precautions to minimise contamination should be taken during all processing stages including the stages before sterilisation.
- 1.11.2 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.
- 1.11.3 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. 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.
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.
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 but a contamination rate of less than 0,1 % with 95 % confidence limit is acceptable.
The manufacturer should establish alert and action limits. Any contamination should be investigated.¹
- 1.11.4 Care should be taken that any validation does not compromise the processes.
- 1.11.5 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.
- 1.11.6 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.
- 1.11.7 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.

¹ For further details on the validation of aseptic processing, please refer to the PIC/S Recommendation on the Validation of Aseptic Processing (PI 007)

1.11 PROCESSING continued

- 1.11.8 Containers and materials liable to generate fibres should be minimised in clean areas.
- 1.11.9 Where appropriate, measures should be taken to minimise the particulate contamination of the end product.
- 1.11.10 Components, containers and equipment should be handled after the final cleaning process in such a way that they are not recontaminated.
- 1.11.11 The interval between the washing and drying and the sterilisation of components, containers and equipment as well as between their sterilization and use should be minimised and subject to a time-limit appropriate to the storage conditions.
- 1.11.12 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.
- 1.11.13 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.
Where appropriate the absence of pyrogens 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.
- 1.11.14 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.
- 1.11.15 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.

1.12 STERILISATION

- 1.12.1 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, British or United States 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 medicine registrations.
- 1.12.2 Before any sterilisation process is adopted its suitability for the product and its efficacy in achieving the desired sterilising conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators where appropriate.
The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.
- 1.12.3 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.
- 1.12.4 Validated loading patterns should be established for all sterilisation processes.
- 1.12.5 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.

1.12 STERILISATION continued

- 1.12.6 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.

- 1.12.7 Sterilisation records should be available for each sterilisation run. They should be approved as part of the batch release procedure.

1.13 STERILISATION BY HEAT

- 1.13.1 Each heat sterilisation cycle should be recorded on a time/temperature chart with a suitably 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.

- 1.13.2 Chemical or biological indicators may also be used, but should not take the place of physical measurements.

- 1.13.3 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.

- 1.13.4 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.

1.14 MOIST HEAT

- 1.14.1 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.

- 1.14.2 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.

- 1.14.3 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.

1.15 DRY HEAT

- 1.15.1 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.

1.16 STERILISATION BY RADIATION

- 1.16.1 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.
- 1.16.2 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.
- 1.16.3 Biological indicators may be used as an additional control.
- 1.16.4 Validation procedures should ensure that the effects of variations in density of the packages are considered.
- 1.16.5 Materials handling procedures should prevent mix-up between irradiated and non-irradiated materials. Radiation-sensitive colour disks should also be used on each package to differentiate between packages which have been subjected to a irradiation and those which have not.
- 1.16.6 The total radiation dose should be administered within a predetermined time span.

1.17 STERILISATION WITH ETHYLENE OXIDE

- 1.17.1 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.
- 1.17.2 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.
- 1.17.3 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.
- 1.17.4 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.

1.17 STERILISATION WITH ETHYLENE OXIDE *continued*

- 1.17.5 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.
- 1.17.6 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.

1.18 FILTRATION OF MEDICINAL PRODUCTS WHICH CANNOT BE STERILISED IN THEIR FINAL CONTAINER

- 1.18.1 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 µm (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.
- 1.18.2 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.
- 1.18.3 Fibre shedding characteristics of filters should be minimal.
- 1.18.4 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 during routine manufacturing from this 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.
- 1.18.5 The same filter should not be used for more than one working day unless such use has been validated.
- 1.18.6 The filter should not affect the product by removal of ingredients from it or by release of substances into it.

1.19 FINISHING OF STERILE PRODUCTS

- 1.19.1 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.
- 1.19.2 Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.

1.19 FINISHING OF STERILE PRODUCTS *continued*

- 1.19.3 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.

1.20 QUALITY CONTROL

- 1.20.1 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.

- 1.20.2 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.

- 1.20.3 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 PRODUCTS FOR HUMAN USE****2.1 SCOPE**

The methods employed in the manufacture of biological medicinal products are a critical factor in shaping the appropriate regulatory control. Biological medicinal products can be defined therefore largely by reference to their method of manufacture.

Biological medicinal products prepared by the following methods of manufacture will fall under the scope of this annex ²:

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

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

Note: In drawing up this Annex, due consideration has been given to the general requirements for manufacturing establishments and control laboratories proposed by the WHO.

This Annex does not lay down detailed requirements for specific classes of biological products.

2.2 PRINCIPLE

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

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

These biological processes may display inherent variability, so that the range and nature of by-products are variable. Moreover, the materials used in these cultivation processes provide good substrates for growth of microbial contaminants.

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

2.2.4 The special properties of biological medicinal products require careful consideration in any code of Good Manufacturing Practice and the development of this annex takes these points into account.

2.3 PERSONNEL

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

² Biological medicinal products manufactured by these methods include: vaccines, immunosera, antigens, hormones, cytokines, enzymes and other products of fermentation (including monoclonal antibodies and products derived from r-DNA).

2.3 PERSONNEL continued

- 2.3.2 Persons responsible for production and quality control should have an adequate background in relevant scientific disciplines, such as bacteriology, biology, biometry, chemistry, medicine, pharmacy, pharmacology, virology, immunology and veterinary medicine, together with sufficient practical experience to enable them to exercise their management function for the process concerned.
- 2.3.3 The immunological status of personnel may have to be taken into consideration for product safety. All personnel engaged in production, maintenance, testing and animal care (and inspectors) should be vaccinated where necessary with appropriate specific vaccines and have regular health checks. Apart from the obvious problem of exposure of staff to infectious agents, potent toxins or allergens, it is necessary to avoid the risk of contamination of a production batch with infectious agents. Visitors should generally be excluded from production areas.
- 2.3.4 Any changes in the immunological status of personnel which could adversely affect the quality of the product should preclude work in the production area. 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.
- 2.3.5 In the course of a working day, personnel should not pass from areas where exposure to live organisms or animals is possible to areas where other products or different organisms are handled. If such passage is unavoidable, clearly defined decontamination measures, including change of clothing and shoes and, where necessary, showering should be followed by staff involved in any such production.

2.4 PREMISES AND EQUIPMENT

- 2.4.1 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 risk to the finished product.
- 2.4.2 The risk of cross-contamination between biological medicinal products, especially during those stages of the manufacturing process in which live organisms are used, may require additional precautions with respect to facilities and equipment, such as the use of dedicated facilities and equipment, production on a campaign basis and the use of closed systems. The nature of the product as well as the equipment used will determine the level of segregation needed to avoid cross-contamination.
- 2.4.3 In principle, dedicated facilities should be used for the production of BCG vaccine and for the handling of live organisms used in production of tuberculin products.
- 2.4.4 Dedicated facilities should be used for the handling of *Bacillus anthracis*, of *Clostridium botulinum* and of *Clostridium tetani* until the inactivation process is accomplished.
- 2.4.5 Production on a campaign basis may be acceptable for other spore forming organisms provided that the facilities are dedicated to this group of products and not more than one product is processed at any one time.
- 2.4.6 Simultaneous production in the same area using closed systems of biofermenters may be acceptable for products such as monoclonal antibodies and products prepared by r-DNA techniques.
- 2.4.7 Processing steps after harvesting may be carried out simultaneously in the same production area provided that adequate precautions are taken to prevent cross-contamination. For killed vaccines and toxoids, such parallel processing should only be performed after inactivation of the culture or after detoxification.
- 2.4.8 Positive pressure areas should be used to process sterile products but negative pressure in specific areas at point of exposure of pathogens is acceptable for containment reasons. Where negative pressure areas or safety cabinets are used for aseptic processing of pathogens, they should be surrounded by a positive pressure sterile zone.

2.4 PREMISES AND EQUIPMENT *continued*

- 2.4.9 Air handling units should be specific to the processing area concerned and recirculation of air should not occur from areas handling live pathogenic organisms.
- 2.4.10 The layout and design of production areas and equipment should permit effective cleaning and decontamination (e.g. by fumigation). The adequacy of cleaning and decontamination procedures should be validated.
- 2.4.11 Equipment used during handling of live organisms should be designed to maintain cultures in a pure state and uncontaminated by external sources during processing.
- 2.4.12 Pipework systems, valves and vent filters should be properly designed to facilitate cleaning and sterilisation.
The use of "clean in place" and "sterilise in place" systems should be encouraged.
Valves on fermentation vessels should be completely steam sterilisable.
Air vent filters should be hydrophobic and validated for their scheduled life span.
- 2.4.13 Primary containment should be designed and tested to demonstrate freedom from leakage risk.
- 2.4.14 Effluents which may contain pathogenic micro-organisms should be effectively decontaminated.
- 2.4.15 Due to the variability of biological products or processes, some additives or ingredients have to be measured or weighed during the production process (e.g. buffers). In these cases, small stocks of these substances may be kept in the production area.

2.5 ANIMAL QUARTERS AND CARE

- 2.5.1 Animals are used for the manufacture of a number of biological products, for example polio vaccine (monkeys), snake antivenoms (horses and goats), rabies vaccine (rabbits, mice and hamsters) and serum gonadotropin (horses). In addition, animals may also be used in the quality control of most sera and vaccines, e.g. pertussis vaccine (mice), pyrogenicity (rabbits), BCG vaccine (guinea-pigs).
- 2.5.2 Quarters for animals used in production and control of biological products should be separated from production and control areas.
The health status of animals from which some starting materials are derived and of those used for quality control and safety testing should be monitored and recorded.
Staff employed in such areas must be provided with special clothing and changing facilities.
Where monkeys are used for the production or quality control of biological medicinal products, special consideration is required as laid down in the current WHO Requirements for Biological Substances No. 7.

2.6 DOCUMENTATION

- 2.6.1 Specifications for biological starting materials may need additional documentation on the source, origin, method of manufacture and controls applied, particularly microbiological controls.
- 2.6.2 Specifications are routinely required for intermediate and bulk biological medicinal products.

2.7 PRODUCTION

2.7.1 Starting materials

- a) The source, origin and suitability of starting materials 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. In such cases, release of a finished product is conditional on satisfactory results of these tests.

2.7.1 Starting materials continued

- b) Where sterilisation 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).

2.7.2 Seed lot and cell bank system

- a) In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of biological medicinal products obtained by microbial culture, cell culture or propagation in embryos and animals should be based on a system of master and working seed lots and/or cell banks.
- b) The number of generations (doublings, passages) between the seed lot or cell bank and the finished product should be consistent with the medicine registration dossier.
Scaling up of the process should not change this fundamental relationship.
- c) Seed lots and cell banks should be adequately characterised and tested for contaminants. Their suitability for use should be further demonstrated by the consistency of the characteristics and quality of the successive batches of product.
Seed lots and cell banks should be established, stored and used in such a way as to minimise the risks of contamination or alteration.
- d) Establishment of the seed lot and cell bank should be performed in a suitably controlled environment to protect the seed lot and the cell bank and, if applicable, the personnel handling it.
During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus, cell lines or cell strains) should be handled simultaneously in the same area or by the same persons.
- e) Evidence of the stability and recovery of the seeds and banks should be documented.
Storage containers should be hermetically sealed, clearly labelled and kept at an appropriate temperature.
An inventory should be meticulously kept.
Storage temperature should be recorded continuously for freezers and properly monitored for liquid nitrogen.
Any deviation from set limits and any corrective action taken should be recorded.
- f) Only authorised personnel should be allowed to handle the material and this handling should be done under the supervision of a responsible person.
Access to stored material should be controlled.
Different seed lots or cell banks should be stored in such a way to avoid confusion or cross-contamination
It is desirable to split the seed lots and cell banks and to store the parts at different locations so as to minimise the risks of total loss.
- g) All containers of master or working cell banks and seed lots should be treated identically during storage. Once removed from storage, the containers should not be returned to the stock.

2.7.3 Operating principles

- a) The growth promoting properties of culture media should be demonstrated.
- b) Addition of materials or cultures to fermenters and other vessels and the taking of samples should be carried out under carefully controlled conditions to ensure that absence of contamination is maintained. Care should be taken to ensure that vessels are correctly connected when addition or sampling take place.
- c) Centrifugation and blending of products can lead to aerosol formation and containment of such activities to prevent transfer of live micro-organisms is necessary.

2.7.3 Operating principles continued

- d) If possible, media should be sterilised *in situ*. In-line sterilising filters for routine addition of gases, media, acids or alkalis, defoaming agents etc. to fermenters should be used where possible.
- e) Careful consideration should be given to the validation of any necessary virus removal or inactivation undertaken.
- f) 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.
- g) A wide variety of equipment is used for chromatography, and in general such equipment should be dedicated to the purification of one product and should be sterilised or sanitised between batches. the use of the same equipment at different stages of processing should be discouraged. Acceptance criteria, life span and sanitization or sterilisation method of columns should be defined.

2.8 QUALITY CONTROL

- 2.8.1 In-process controls play a specially important role in ensuring the consistency of the quality of biological medicinal products. Those controls which are crucial for quality (e.g. virus removal) but which cannot be carried out on the finished product, should be performed at an appropriate stage of production.
- 2.8.2 It may be necessary to retain samples of intermediate products in sufficient quantities and under appropriate storage conditions to allow the repetition or confirmation of a batch control.
- 2.8.3 Continuous monitoring of certain production processes is necessary, for example fermentation. Such data should form part of the batch record.
- 2.8.4 Where continuous culture is used, special consideration should be given to the quality control requirements arising from this type of production method.

ANNEX 3

MANUFACTURE OF RADIOPHARMACEUTICALS

3.1 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 radiopharmacies (hospitals or certain pharmacies), using Generators and Kits manufactured in terms of the Provisions of Section 14(4) of the medicines and Related substances Act, 1965 (Act 101 of 1965) i.e. Extemporaneous compounding in terms of small scale manufacturing of medicines, 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 practitioner. 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 International Atomic Energy Association (IAEA) and radiation protection requirements.

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

3.2 INTRODUCTION

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.

Due to their short half-life, some radiopharmaceuticals are released before completion of certain Quality Control tests. In this case, the continuous assessment of the effectiveness of the Quality Assurance system becomes very important.

Care should be taken to comply with national and local regulations concerning production, supply, storage, use and disposal of radioactive products.

Radiopharmaceuticals, produced by a nuclear reactor or cyclotron, may only be used by physicians who are qualified by specific training in the safe use and handling of radioisotopes, and whose experience and training have been approved by an appropriate governmental agency authorised to licence the use of radionuclides.

Note: The manufacture of radiopharmaceuticals in South Africa must comply with

- the requirements of Act 15 of 1973 (Hazardous Substances Act), regulation R247 of 26 February 1993 and
- any directives issued by the Directorate Radiation Control of the South African Department of Health, e.g. those specifying the basic standards for health protection of the general public and workers against the dangers of ionising radiation.

3.2 INTRODUCTION continued

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	<i>Reactor/Cyclotron Production</i>	Chemical synthesis	Purification steps	Processing, formulation and dispensing	Aseptic or final sterilization
Radionuclide Generators	<i>Reactor/Cyclotron Production</i>	Processing			

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

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.

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 the GMP Guide, Annex 1.

Specifications and quality control testing procedures for the most commonly used radiopharmaceuticals are specified in the Pharmacopoeia or in the marketing authorisation.

Radiopharmaceuticals intended for use in clinical trials as investigational medicinal products should in addition be produced in accordance with the principles of GMP (part I or II).

3.3 QUALITY ASSURANCE

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.

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.

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.

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.

3.4 PERSONNEL

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 Pharmacist should have the overall responsibility for release of the products.

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.

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.

All people engaged in radioactive work are required by law to be registered as radiation workers. Maximum permitted radiation doses for radiation workers are prescribed by the International Atomic Energy Agency and are monitored by film badges and pocket dosimeters or TLD. At all times the ALARA principle (i.e. as low as reasonably attainable dose) applies to any person working with radioactivity.

3.5 PREMISES AND EQUIPMENT

- 3.5.1 Premises in which radioactive work is conducted must be licensed by the Department of Health.
- 3.5.2 Radioactive products should be manufactured and controlled (environmental and radioactive) areas. All manufacturing steps should take place in self-contained facilities dedicated to radiopharmaceuticals.
- 3.3.3 In order to contain the radioactivity, it may be necessary for the air pressure to be lower where products are exposed than in 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.
- 3.3.4 Air extracted from areas where radioactive products are handled should not be recirculated; air outlets should be designed to minimize environmental contamination of radioactive particles and gases and appropriate measures should be taken to protect the controlled areas from particulate and microbial contamination.
- 3.3.5 Re-circulation of air extracted from area where radioactive products are handled should be avoided unless justified. There should be a system to prevent air entering the clean area through extract ducts e.g. when the extract fan is not operating.
- 3.3.5 Measures should be established and implemented to prevent cross-contamination from personnel, materials, radionuclides etc. 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.
- 3.3.6 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.
- 3.3.7 Access to the manufacturing areas should be via a gowning area and should be restricted to authorised personnel.
- 3.3.8 Workstations and their environment should be monitored with respect to radioactivity, particulate and microbiological quality as established during performance qualification (PQ)
- 3.3.9 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.

3.5 PREMISES AND EQUIPMENT continued

- 3.3.10 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.
- 3.3.11 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.
- 3.3.12 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.
- 3.3.13 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
- 3.3.14 For manufacture of radiopharmaceuticals a risk assessment may be applied to determine the appropriate pressure differences, air flow direction and air quality.

3.6 DOCUMENTATION

- 3.6.1 All documents related to the manufacture of radiopharmaceuticals should be prepared, reviewed, approved and distributed according to written procedures.
- 3.6.2 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.
- 3.6.3 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).
- 3.6.4 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.
- 3.6.5 Records should be retained for at least 3 years unless another timeframe is specified in national requirements.

3.7 PRODUCTION

- 3.7.1 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.
- 3.7.2 Special attention should be paid to validation including validation of computerised systems which should be carried out in accordance in compliance with the GMP Guide, Annex 11. New manufacturing processes should be validated prospectively.
- 3.7.3 The critical parameters should normally be identified before or during validation and the ranges necessary for reproducible operation should be defined.
- 3.7.4 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.
- 3.7.5 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.

3.8 QUALITY CONTROL

- 3.8.1 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.
- 3.8.2 Radiopharmaceutical product release may be carried out in two or more stages, before and after full analytical testing.
- 3.8.3 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.
- 3.8.4 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 Pharmacist. Where certain test results are not available before use of the product, the Responsible Pharmacist should conditionally certify the product before it is used and should finally certify the product after all the test results are obtained.
- 3.8.5 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.
- 3.8.6 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 Pharmacist.
- 3.8.7 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.
- 3.8.8 A written procedure detailing the assessment of production and analytical data, which should be considered before the batch is dispatched, should be established.
- 3.8.9 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.
- 3.8.10 A procedure should also describe the measures to be taken by the Responsible Pharmacist 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.
- 3.8.11 This process must be documented.
- 3.8.12 Information should be given to the clinical responsible persons, if necessary. To facilitate this, a traceability system should be implemented for radiopharmaceuticals.
- 3.8.13 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.

3.9 REFERENCE AND RETENTION SAMPLES

- 3.9.1 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.
- 3.9.2 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 the product. That period may be shortened if the period of stability of the material as indicated in the relevant specification is shorter.
- 3.9.3 Other conditions may be defined by the Medicines Control Council for the sampling and retaining of starting materials and products manufactured individually or in small quantities or when their storage could raise special problems as per the product registration.

3.10 DISTRIBUTION

- 3.10.1 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.

3.11 GLOSSARY

Preparation: handling and radiolabelling of kits with radionuclide eluted from generators or radioactive precursors within a hospital. Kits, generators and precursors should be registered or licensed by the Medicines Control council as the case may be.

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.

ANNEX 4

MANUFACTURE OF VETERINARY MEDICINAL PRODUCTS OTHER THAN IMMUNOLOGICALS

4.1 MANUFACTURE OF PREMIXES FOR MEDICATED FEEDING STUFFS

For the purposes of these paragraphs,

- a *medicated feeding stuff* is any mixture of a veterinary medicinal product or products and feed or feeds which is ready prepared for marketing and intended to be fed to animals without further processing because of its curative or preventative properties or other properties (e.g. medical diagnosis, restoration, correction or modification of physiological functions in animals):
- a *pre-mix for medicated feeding stuffs* is any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feeding stuffs.

- 4.1.1 The manufacture of premixes for medicated feeding stuffs requires the use of large quantities of vegetable matter which is likely to attract insects and rodents. Premises should be designed, equipped and operated to minimize this risk (Chapter 3 item 3.2.1 (iv)) and should also be subject to a regular pest control programme.
- 4.1.2 Because of the large volume of dust generated during the production of bulk material for premixes, specific attention should be given to the need to avoid cross contamination and facilitate cleaning (Chapter 3 item 3.2.2. (ix)), for example through the installation of sealed transport systems and dust extraction, whenever possible. The installation of such systems does not, however, eliminate the need for regular cleaning of production areas.
- 4.1.3 Parts of the process likely to have a significant adverse influence on the stability of the active ingredients (e.g. use of steam in pellet manufacture) should be carried out in a uniform manner from batch to batch.
- 4.1.4 Consideration should be given to undertake the manufacture of premixes in dedicated areas which, if at all possible, do not form part of a main manufacturing plant. Alternatively, such dedicated areas should be surrounded by a buffer zone in order to minimize the risk of contamination of other manufacturing areas.

4.2 THE MANUFACTURE OF ECTOPARASITICIDES

- 4.2.1 In derogation from Chapter 3 item 3.2.2 (i) ectoparasiticides for external application to animals, which are veterinary medicinal products, and subject to medicine registration, may be produced and filled on a campaign basis in pesticide specific areas. However, other categories of veterinary medicinal products should not be produced in such areas.
- 4.2.2 Adequate validated cleaning procedures should be employed to prevent cross contamination, and steps should be taken to ensure the secure storage of the veterinary medicinal product in accordance with the guide.

4.3 THE MANUFACTURE OF VETERINARY MEDICINAL PRODUCTS CONTAINING PENICILLINS

The use of penicillins in veterinary medicine does not present the same risks of hypersensitivity in animals as in humans. Although incidents of hypersensitivity have been recorded in horses and dogs, there are other materials which are toxic to certain species, e.g. the ionophore antibiotics in horses. Although desirable, the requirements that such products be manufactured in dedicated, self-contained facilities (Chapter 3 item 3.2.2 (i)) may be dispensed with in the case of facilities dedicated to the manufacture of veterinary medicinal products only. However, all necessary measures should be taken to avoid cross-contamination and any risk to operator safety in accordance with the guide. In such circumstances, penicillin-containing products should be manufactured on a campaign basis and should be followed by appropriate, validated decontamination and cleaning procedures.

4.4 RETENTION OF SAMPLES (Chapter 1 item 1.4.2 (viii) and Chapter 6 item 6.5.4)

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

4.5 STERILE VETERINARY MEDICINAL PRODUCTS

Where this has been accepted by the Medicines Control Council, terminally sterilized veterinary medicinal products may be manufactured in a clean area of a lower grade than the grade required in the annex on "Sterile preparations", but at least in a grade D environment.

ANNEX 5**MANUFACTURE OF IMMUNOLOGICAL VETERINARY MEDICAL PRODUCTS****5.1 PRINCIPLE**

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

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

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

5.2 PERSONNEL

- 5.2.1 All personnel (including those concerned with cleaning and maintenance) employed in areas where immunological products are manufactured should be given training in and information on hygiene and microbiology. They should receive additional training specific to the products with which they work.
- 5.2.2 Responsible personnel should be formally trained in some or all of the following fields: bacteriology, biology, biometry, chemistry, immunology, medicine, parasitology, pharmacy, pharmacology, virology and veterinary medicine and should also have an adequate knowledge of environmental protection measures.
- 5.2.3 Personnel should be protected against possible infection with the biological agents used in manufacture. In the case of biological agents known to cause disease in humans, adequate measures should be taken to prevent infection of personnel working with the agent or with experimental animals. Where relevant, the personnel should be vaccinated and subject to medical examination.
- 5.2.4 Adequate measures should be taken to prevent biological agents being taken outside the manufacturing plant by personnel acting as a carrier. Dependent on the type of biological agent, such measures may include complete change of clothes and compulsory showering before leaving the production area.
- 5.2.5 For immunological products, the risk of contamination or cross-contamination by personnel is particularly important.

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

Prevention of cross-contamination by personnel involved in production should be achieved by a set of measures and procedures to ensure that they do not pass from one area to another unless they have taken appropriate measures to eliminate the risk of contamination.

5.2 PERSONNEL *continued*

In the course of a working day, personnel should not pass from areas where contamination with live micro-organisms is likely or where animals are housed to premises where other products or organisms are handled. If such a passage is unavoidable, clearly defined decontamination procedures, including change of clothing and shoes, and, where necessary, showering, should be followed by staff involved in any such production.

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

5.3 PREMISES

5.3.1 Premises should be designed in such a way as to control both the risk to the product and to the environment.

This can be achieved by the use of containment, clean, clean/contained or controlled areas.

5.3.2 Live biological agents should be handled in contained areas. The level of containment should depend on the pathogenicity of the micro-organism and whether it has been classified as exotic.

5.3.3 Inactivated biological agents should be handled in clean areas.

Clean areas should also be used when handling non-infected cells isolated from multicellular organisms and, in some cases, filtration-sterilized media.

5.3.4 Open circuit operations involving products or components not subsequently sterilized should be carried out within a laminar air flow work station (grade A) in a grade B area.

5.3.5 Other operations where live biological agents are handled (quality control, research and diagnostic services, etc.) should be appropriately, contained and separated if production operations are carried out in the same building. The level of containment should depend on the pathogenicity of the biological agent and whether they have been classified as exotic.

Whenever diagnostic activities are carried out, there is the risk of introducing highly pathogenic organisms. Therefore, the level of containment should be adequate to cope with all such risks.

Containment may also be required if quality control or other activities are carried out in buildings in close proximity to those used for production.

5.3.6 Containment premises should be easily disinfected and should have the following characteristics:

- (a) the absence of direct venting to the outside;
- (b) a ventilation with air at negative pressure.

Air should be extracted through HEPA filters and not be recirculated except to the same area, and provided further HEPA filtration is used (normally this condition would be met by routing the recirculated air through the normal supply HEPAs for that area). However, recycling of air between areas may be permissible provided that it passes through two exhaust HEPAs, the first of which is continuously monitored for integrity, and there are adequate measures for safe venting of exhaust air should this filter fail;

- (c) air from manufacturing areas used for the handling of exotic organisms should be vented through 2 sets of HEPA filters in series, and that from production areas not recirculated;
- (d) a system for the collection and disinfection of liquid effluents including contaminated condensate from sterilizers, biogenerators, etc. Solid wastes, including animal carcasses, should be disinfected, sterilized or incinerated as appropriate. Contaminated filters should be removed using a safe method;
- (e) changing rooms designed and used as air locks, and equipped with washing and showering facilities if appropriate. Air pressure differentials should be such that there is no flow of air between the work area and the external environment or risk of contamination of outer clothing worn outside the area;

5.3 PREMISES *continued*

- (f) an air lock system for the passage of equipment, which is constructed so that there is no flow of contaminated air between the work area and the external environment or risk of contamination of equipment within the lock. The air lock should be of a size which enables the effective surface decontamination of materials being passed through it. Consideration should be given to having a timing device on the door interlock to allow sufficient time for the decontamination process to be effective;
- (g) in many instances, a barrier double-door autoclave for the secure removal of waste materials and introduction of sterile items.

5.3.7 Equipment passes and changing rooms should have an interlock mechanism or other appropriate system to prevent the opening of more than one door at a time.

Changing rooms should be supplied with air filtered to the same standard as that for the work area, and extracts to produce an adequate air circulation independent of that of the work area.

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

5.3.8 Production operations such as cell maintenance, media preparation, virus culture, etc. likely to cause contamination should be performed in separate areas.

Animals and animal products should be handled with appropriate precautions.

5.3.9 Production areas where biological agents particularly resistant to disinfection (e.g. spore-forming bacteria) are handled should be separated and dedicated to that particular purpose until the biological agents have been inactivated.

5.3.10 With the exception of blending and subsequent filling operations, one biological agent only should be handled at a time within an area.

5.3.11 Production areas should be designed to permit disinfection between campaigns, using validated methods.

5.3.12 Production of biological agents may take place in controlled areas provided it is carried out in totally enclosed and heat sterilized equipment, all connections being also heat sterilized after making and before breaking. It may be acceptable for connections to be made under local laminar air flow provided these are few in number and proper aseptic techniques are used and there is no risk of leakage.

The sterilization parameters used before breaking the connections must be validated for the organisms being used.

Different products may be placed in different biogenerators, within the same area, provided that there is no risk of accidental cross-contamination. However, organisms generally subject to special requirements for containment should be in areas dedicated to such products.

5.3.13 Animal houses where animals intended or used for production are accommodated, should be provided with the appropriate containment and/or clean area measures, and should be separate from other animal accommodation.

Animal houses where animals used for quality control, involving the use of pathogenic biological agents, are accommodated, should be adequately contained.

5.3.14 Access to manufacturing areas should be restricted to authorized personnel. Clear and concise written procedures should be posted as appropriate.

5.3.15 Documentation relating to the premises should be readily available in a plant master file.

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

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

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

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

5.4 EQUIPMENT

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

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

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

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

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

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

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

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

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

All sterilization procedures should be validated.

- 5.4.5 Equipment should be designed so as to prevent any mix-up between different organisms or products.

Pipes, valves and filters should be identified as to their function.

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

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

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

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

- 5.4.7 The loading of freeze driers requires an appropriate clean/contained area.

Unloading freeze driers contaminates the immediate environment. Therefore, for single-ended freeze driers, the clean room should be decontaminated before a further manufacturing batch is introduced into the area, unless this contains the same organisms, and double door freeze driers should be sterilized after each cycle unless opened in a clean area.

Sterilization of freeze driers should be done in accordance with item 5.4.3. In case of campaign working, they should at least be sterilized after each campaign.

5.5 ANIMALS AND ANIMAL HOUSES

- 5.5.1 Animal houses should be separated from the other production premises and suitably designed.
- 5.5.2 The sanitary status of the animals used for production should be defined, monitored, and recorded. Some animals should be handled as defined in specific monographs (e.g. Specific Pathogens Free flocks).
- 5.5.3 Animals, biological agents, and tests carried out should be the subject of an identification system so as to prevent any risk of confusion and to control all possible hazards.

5.6 DISINFECTION - WASTE DISPOSAL

Disinfection and/or wastes and effluents disposal may be particularly important in the case of manufacture of immunological products. Careful consideration should therefore be given to procedures and equipment aiming at avoiding environmental contamination as well as to their validation and qualification.

5.7 PRODUCTION

Because of the wide variety of products, the frequently large number of stages involved in the manufacture of immunological veterinary medicinal products and the nature of the biological processes, careful attention must be paid to adherence to validated operating procedures, to the constant monitoring of production at all stages and to in-process controls.

Additionally, special consideration should be given to starting materials, media and the use of a seed lot system.

5.8 STARTING MATERIALS

- 5.8.1 The suitability of starting materials should be clearly defined in written specifications. These should include details of the supplier, the method of manufacture, the geographical origin and the animal species from which the materials are derived. The controls to be applied to starting materials must be included. Microbiological controls are particularly important.
- 5.8.2 The results of tests on starting materials must comply with the specifications.
- 5.8.3 Where the tests take a long time (e.g. eggs from SPF flocks) it may be necessary to process starting materials before the results of analytical controls are available. In such cases, the release of a finished product is conditional upon satisfactory results of the tests on starting materials.
- 5.8.4 Special attention should be paid to a knowledge of the supplier's quality assurance system in assessing the suitability of a source and the extent of quality control testing required.
- 5.8.5 Where possible, heat is the preferred method for sterilizing starting materials. If necessary, other validated methods, such as irradiation, may be used.
- 5.8.6 *Media*
 - a) The ability of media to support the desired growth should be properly validated in advance.
 - b) Media should preferably be sterilized *in situ* or in line. Heat is the preferred method. Gases, media, acids, alkalis, defoaming agents and other materials introduced into sterile bioreactors should themselves be sterile.
- 5.8.7 *Seed lot and cell bank system*
 - a) In order to prevent the unwanted drift of properties which might ensue from repeated subcultures or multiple generations, the production of immunological veterinary medicinal products obtained by microbial, cell or tissue culture, or propagation in embryos and animals, should be based on a system of seed lots and/or cell banks.

5.8.7 *Seed lot and cell bank system continued*

- b) The number of generations (doublings, passages) between the seed lot or cell bank and the finished product should be consistent with the dossier of authorization for marketing.
- c) Seed lots and cell banks should be adequately characterized and tested for contaminants. Acceptance criteria for new seed lots shall be established. Seed lots and cell banks shall be established, stored and used in such a way as to minimize the risks of contamination, or any alteration. During the establishment of the seed lot and cell bank, no other living or infectious material (e.g. virus or cell lines) shall be handled simultaneously in the same area or by the same person.
- d) Establishment of the seed lot and cell bank should be performed in a suitable environment to protect the seed lot and the cell bank and, if applicable, the personnel handling it and the external environment.
- e) The origin, form and storage conditions of seed material should be described in full.
Evidence of the stability and recovery of the seeds and banks should be provided.
Storage containers should be hermetically sealed, clearly labelled and stored at an appropriate temperature.
Storage conditions shall be properly monitored. An inventory should be kept and each container accounted for.
- f) Only authorized personnel should be allowed to handle the material and this handling should be done under the supervision of a responsible person.
Different seed lots or cell banks shall be stored in such a way to avoid confusion or cross-contamination errors. It is desirable to split the seed lots and cell banks and to store the parts at different locations so as to minimize the risk of total loss.

5.8.8 *Operating principles*

- a) The formation of droplets and the production of foam should be avoided or minimized during manufacturing processes.
Centrifugation and blending procedures which can lead to droplet formation should be carried out in appropriate contained or clean/contained areas to prevent transfer of live organisms.
- b) Accidental spillages, especially of live organisms, must be dealt with quickly and safely.
Validated decontamination measures should be available for each organism.
Where different strains of single bacteria species or very similar viruses are involved, the process need be validated against only one of them, unless there is reason to believe that they may vary significantly in their resistance to the agent(s) involved.
- c) Operations involving the transfer of materials such as sterile media, cultures or product should be carried out in pre-sterilized closed systems wherever possible.
Where this is not possible, transfer operations must be protected by laminar airflow work stations.
- d) Addition of media or cultures to biogenerators and other vessels should be carried out under carefully controlled conditions to ensure that contamination is not introduced.
Care must be taken to ensure that vessels are correctly connected when addition of cultures takes place.
- e) When necessary, for instance when two or more fermentors are within a single area, sampling and addition ports, and connectors (after connection, before the flow of product, and again before disconnection) should be sterilized with steam. In other circumstances, chemical disinfection of ports and laminar air flow protection of connections may be acceptable.
- f) Equipment, glassware, the external surfaces of product containers and other such materials must be disinfected before transfer from a contained area using a validated method (see 5.8.8b above).

5.8.8 *Operating principles continued*

Batch documentation can be a particular problem. Only the absolute minimum required to allow operations to GMP standards should enter and leave the area. If obviously contaminated, such as by spills or aerosols, or if the organism involved is an exotic, the paperwork must be adequately disinfected through an equipment pass, or the information transferred out by such means as photocopy or fax.

- g) Liquid or solid wastes such as the debris after harvesting eggs, disposable culture bottles, unwanted cultures or biological agents, are best sterilized or disinfected before transfer from a contained area.
However, alternatives such as sealed containers or piping may be appropriate in some cases.
- h) Articles and materials, including documentation, entering a production room should be carefully controlled to ensure that only materials concerned with production are introduced. There should be a system which ensures that materials entering a room are reconciled with those leaving so that accumulation of materials within the room does not occur.
- i) Heat stable articles and materials entering a clean area or clean/contained area should do so through a double-ended autoclave or oven.
Heat labile articles and materials should enter through an airlock with interlocked doors where they are disinfected.
Sterilization of articles and materials elsewhere is acceptable provided that they are double wrapped and enter through an airlock with the appropriate precautions.
- j) Precautions must be taken to avoid contamination or confusion during incubation. There should be a cleaning and disinfection procedure for incubators. Containers in incubators should be carefully and clearly labelled.
- k) With the exception of blending and subsequent filling operations (or when totally enclosed systems are used) only one live biological agent may be handled within a production room at any given time. Production rooms must be effectively disinfected between the handling of different live biological agents.
- l) Products should be inactivated by the addition of inactivant accompanied by sufficient agitation. The mixture should then be transferred to a second sterile vessel, unless the container is of such a size and shape as to be easily inverted and shaken so as to wet all internal surfaces with the final culture/ inactivant mixture.
- m) Vessels containing inactivated product should not be opened or sampled in areas containing live biological agents. All subsequent processing of inactivated products should take place in clean areas grade A-B or enclosed equipment dedicated to inactivated products.
- n) Careful consideration should be given to the validation of methods for sterilization, disinfection, virus removal and inactivation.
- o) Filling should be carried out as soon as possible following production.
Containers of bulk product prior to filling should be sealed, appropriately labelled and stored under specified conditions of temperature.
- p) There should be a system to assure the integrity and closure of containers after filling.
- q) The capping of vials containing live biological agents must be performed in such a way that ensures that contamination of other products or escape of the live agents into other areas or the external environment does not occur.
- r) For various reasons there may be a delay between the filling of final containers and their labelling and packaging. Procedures should be specified for the storage of unlabelled containers in order to prevent confusion and to ensure satisfactory storage conditions.
Special attention should be paid to the storage of heat labile or photosensitive products.
Storage temperatures should be specified.
- s) For each stage of production, the yield of product should be reconciled with that expected from that process. Any significant discrepancies should be investigated.

5.9 QUALITY CONTROL

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

ANNEX 6

MANUFACTURE OF MEDICINAL GASES

6.1 PRINCIPLE

This annexure deals with industrial manufacturing of medicinal gases, which is a specialised industrial process not normally undertaken by pharmaceutical companies. It does not cover manufacturing and handling of medicinal gases in hospitals, which will be subject to national legislation. However relevant parts of this annexure may be used as a basis for such activities.

The manufacture of medicinal gases is generally carried out in closed equipment. Consequently, environmental contamination of the product is minimal. However, there is a risk of cross-contamination with other gases.

Manufacture of medicinal gases should comply with the basic requirements of GMP, with applicable annexes, Pharmacopoeial standards and the following detailed guidelines.

6.2 PERSONNEL

6.2.1 The authorised person responsible for release of medicinal gases should have a thorough knowledge of the production and control of medicinal gases.

6.2.2 All personnel involved in the manufacture of medicinal gases should understand the GMP requirements relevant to medicinal gases and should be aware of the critically important aspects and potential hazards for patients from products in the form of medicinal gases.

6.3 PREMISES AND EQUIPMENT**6.3.1 Premises**

6.3.1.1 Medicinal gases should be filled in a separate area from non-medicinal gases and there should be no exchange of containers between these areas. In exceptional cases, the principal of campaign filling in the same area can be accepted provided that specific precautions are taken and necessary validation is done.

6.3.1.2 Premises should provide sufficient space for manufacturing, testing and storage operations to avoid the risk of mix-up. Premises should be clean and tidy to encourage orderly working and adequate storage.

6.3.1.3 Filling areas should be of sufficient size and have an orderly layout to provide:

- a) separate marked areas for different gases
- b) clear identification and segregation of empty cylinders and cylinders at various stages of processing (e.g. "awaiting filling", "filled", "quarantine", "approved", "rejected").

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

6.3.2 Equipment

6.3.2.1 All equipment for manufacture and analyses should be qualified and calibrated regularly as appropriate.

6.3.2.2 It is necessary to ensure that the correct gas is put into the correct container.

Except for validated automated filling processes there should be no interconnections between pipelines carrying different gases. The manifolds should be equipped with fill connections that correspond only to the valve for that particular gas or particular mixture of gases so that only the correct containers can be attached to the manifold. (The use of manifold and container valve connections may be subject to international or national standards.)

6.3.2 Equipment continued

6.3.2.3 Repair and maintenance operations should not affect the quality of the medicinal gases.

6.3.2.4 Filling of non-medicinal gases should be avoided in areas and with equipment destined for the production of medicinal gases.

Exceptions can be acceptable if the quality of the gas used for non-medicinal purposes is at least equal to the quality of the medicinal gas and GMP-standards are maintained.

There should be a validated method of backflow prevention in the line supplying the filling area for non-medicinal gases to prevent contamination of the medicinal gas.

6.3.2.5 Storage tanks and mobile delivery tanks should be dedicated to one gas and a well-defined quality of this gas. However liquefied medicinal gases may be stored or transported in the same tanks as the same non-medicinal gas provided that the quality of the latter is at least equal to the quality of the medicinal gas.

6.4 DOCUMENTATION

Data included in the records for each batch of cylinders filled must ensure that each filled cylinder is traceable to significant aspects of the relevant filling operations.

As appropriate, the following should be entered:

- the name of the product;
- the date and the time of the filling operations;
- a reference to the filling station used;
- equipment used;
- name and reference to the specification of the gas or each gas in a mixture;
- pre filling operations performed (see below point 6.5.2.5);
- the quantity and size of cylinders before and after filling;
- the name of the person carrying out the filling operation;
- the initials of the operators for each significant step (line clearance, receipt of cylinders, emptying of cylinders etc);
- key parameters that are needed to ensure correct fill at standard conditions;
- the results of quality control tests and where test equipment is calibrated before each test, the reference gas specification and calibration check results;
- results of appropriate checks to ensure the containers have been filled;
- a sample of the batch code label;
- details of any problems or unusual events, and signed authorisation for any deviation from filling instructions;
- to indicate agreement, the date and signature of the supervisor responsible for the filling operation.

6.5 PRODUCTION

All critical steps in the different manufacturing processes should be subject to validation.

6.5.1 Bulk production

6.5.1.1 Bulk gases intended for medicinal use could be prepared by chemical synthesis or obtained from natural resources followed by purification steps if necessary (as for example in an air separation plant). These gases could be regarded as Active Pharmaceutical Ingredients (API) or as bulk pharmaceutical products as decided by the Medicines Control Council.

6.5.1 Bulk production continued

- 6.5.1.2 Documentation should be available specifying the purity, other components and possible impurities that may be present in the source gas and at purification steps, as applicable. Flow charts of each different process should be available.
- 6.5.1.3 All separation and purification steps should be designed to operate at optimal effectiveness.
- 6.5.1.4 For example, impurities that may adversely affect a purification step should be removed before this step is reached.
- 6.5.1.5 Separation and purification steps should be validated for effectiveness and monitored according to the results of the validation.
Where necessary, in-process controls should include continuous analysis to monitor the process. Maintenance and replacement of expendable equipment components, e.g. purification filters, should be based on the results of monitoring and validation.
- 6.5.1.6 If applicable, limits for process temperatures should be documented and in-process monitoring should include temperature measurement.
- 6.5.1.7 Computer systems used in controlling or monitoring processes should be validated.
- 6.5.1.8 For continuous processes, a definition of a batch should be documented and related to the analysis of the bulk gas.
- 6.5.1.9 Gas production should be continuously monitored for quality and impurities.
- 6.5.1.10 Water used for cooling during compression of air should be monitored for microbiological quality when in contact with the medicinal gas.
- 6.5.1.11 All the transfer operations, including controls before transfers, of liquefied gases from primary storage should be in accordance with written procedures designed to avoid any contamination.
- 6.5.1.12 The transfer line should be equipped with a non-return valve or any other suitable alternative. Particular attention should be paid to purge the flexible connections and to coupling hoses and connectors.
- 6.5.1.13 Deliveries of gas may be added to bulk storage tanks containing the same gas from previous deliveries.
The results of a sample must show that the quality of the delivered gas is acceptable.
Such a sample could be taken from:
 - the delivered gas before the delivery is added; or
 - from the bulk tank after adding and mixing.
- 6.5.1.14 Bulk gases intended for medicinal use should be defined as a batch, controlled in accordance with relevant Pharmacopoeial monographs and released for filling.

6.5.2 Filling and labelling

- 6.5.2.1 For filling of medicinal gases the batch should be defined.
- 6.5.2.2 Containers for medicinal gases should conform to appropriate technical specifications.
Valve outlets should be equipped with tamper-evident seals after filling.
Cylinders should preferably have minimum pressure retention valves in order to get adequate protection against contamination.
- 6.5.2.3 The medicinal gases filling manifold as well as the cylinders should be dedicated to a single medicinal gas or to a given mixture of medicinal gases (see also 6.3.2.2 above).
There should be a system in place ensuring traceability of cylinders and valves.
- 6.5.2.4 Cleaning and purging of filling equipment and pipelines should be carried out according to written procedures. This is especially important after maintenance or breaches of system integrity.
Checks for the absence of contaminants should be carried out before the line is released for use.
Records should be maintained.

6.5.2 Filling and labelling continued

6.5.2.5 Cylinders should be subject to an internal visual inspection when

- they are new
- in connection with any hydrostatic pressure test or equivalent test.

After fitting of the valve, the valve should be maintained in a closed position to prevent any contamination from entering the cylinder.

6.5.2.6 Checks to be performed before filling should include:

- a check to determine the residual pressure (>3 to 5 bar) to ensure that the cylinder is not emptied;
- cylinders with no residual pressure should be put aside for additional measures to make sure they are not contaminated with water or other contaminants. These could include cleaning with validated methods or visual inspection as justified;
- assuring that all batch labels and other labels if damaged have been removed;
- visual external inspection of each valve and container for dents, arc burns, debris, other damage and contamination with oil or grease; cylinders should be cleaned, tested and maintained in an appropriate manner;
- a check of each cylinder or cryogenic vessel valve connection to determine that it is the proper type for the particular medicinal gas involved;
- a check of the cylinder "test code date" to determine that the hydrostatic pressure test or equivalent test has been conducted and still is valid as required by national or international guidelines;
- a check to determine that each container is colour-coded according to the relevant standard.

6.5.2.7 Cylinders which have been returned for refilling should be prepared with great care in order to minimise risks for contamination.

For compressed gases a maximum theoretical impurity of 500 ppm v/v should be obtained for a filling pressure of 200 bar (and equivalent for other filling pressures).

Cylinders could be prepared as follows:

- any gas remaining in the cylinders should be removed by evacuating the container (at least to a remaining absolute pressure of 150 millibar)
- or
- by blowing down each container, followed by purging using validated methods (partial pressurisation at least to 7 bar and then blowing down).

For cylinders equipped with residual (positive) pressure valves, one evacuation under vacuum at 150 millibar is sufficient if the pressure is positive.

As an alternative, full analysis of the remaining gas should be carried out for each individual container.

6.5.2.8 There should be appropriate checks to ensure that containers have been filled.

6.5.2.9 An indication that it is filling properly could be to ensure that the exterior of the cylinder is warm by touching it lightly during filling.

6.5.2.10 Each cylinder should be labelled and colour-coded. The batch number and/or filling date and expiry date may be on a separate label.

6.6 QUALITY CONTROL

6.6.1 Water used for hydrostatic pressure testing should be at least of drinking water quality and monitored routinely for microbiological contamination.

6.6.2 Each medicinal gas should be tested and released according to its specifications.

In addition, each medicinal gas should be tested to full relevant pharmacopoeial requirements at sufficient frequency to assure ongoing compliance.

6.6 QUALITY CONTROL continued

- 6.6.3 The bulk gas supply should be released for filling (see 6.5.1.12 above).
- 6.6.4 In the case of a single medicinal gas filled via a multi-cylinder manifold, at least one cylinder of product from each manifold filling should be tested for identity, assay and if necessary water content each time the cylinders are changed on the manifold.
- 6.6.5 In the case of a single medicinal gas filled into cylinders one at a time by individual filling operations, at least one cylinder of each uninterrupted filling cycle should be tested for identity and assay. An example of an uninterrupted filling operation cycle is one shift's production using the same personnel, equipment, and batch of bulk gas.
- 6.6.6 In the case of a medicinal gas produced by mixing two or more different gases in a cylinder from the same manifold, at least one cylinder from each manifold filling operation cycle should be tested for identity, assay and if necessary water content of all of the component gases and for identity of the balancegas in the mixture. When cylinders are filled individually, every cylinder should be tested for identity and assay of all of the component gases and at least one cylinder of each uninterrupted filling cycle should be tested for identity of the balancegas in the mixture.
- 6.6.7 When gases are mixed in-line before filling (e.g. nitrous oxide/oxygen mixture) continuous analysis of the mixture being filled is required.
- 6.6.8 When a cylinder is filled with more than one gas, the filling process must ensure that the gases are correctly mixed in every cylinder and are fully homogeneous.
- 6.6.9 Each filled cylinder should be tested for leaks using an appropriate method, prior to fitting the tamper evident seal. Where sampling and testing is carried out the leak test should be completed after testing.
- 6.6.10 In the case of cryogenic gas filled into cryogenic home vessels for delivery to users, each vessel should be tested for identity and assay.
- 6.6.11 Cryogenic vessels which are retained by customers and where the medicinal gas is refilled in place from dedicated mobile delivery tanks need not be sampled after filling provided the filling company delivers a certificate of analysis for a sample taken from the mobile delivery tank. Cryogenic vessels retained by customers should be periodically tested to confirm that the contents comply with pharmacopoeial requirements.
- 6.6.12 Retained samples are not required, unless otherwise specified.

6.7 STORAGE AND RELEASE

- 6.7.2 Filled cylinders should be held in quarantine until released by the authorized person.
- 6.7.3 Gas cylinders should be stored under cover and not be subjected to extremes of temperature. Storage areas should be clean, dry, well ventilated and free of combustible materials to ensure that cylinders remain clean up to the time of use.
- 6.7.4 Storage arrangements should permit segregation of different gases and of full/empty cylinders and permit rotation of stock on a first in – first out basis.
- 6.7.5 Gas cylinders should be protected from adverse weather conditions during transportation. Specific conditions for storage and transportation should be employed for gas mixtures for which phase separation occurs on freezing.

GLOSSARY

Definition of terms relating to manufacture of medicinal gases, which are not given in the glossary of the current SA Guide to GMP, but which are used in this Annex are given below.

Air separation plant

Air separation plants take atmospheric air and through processes of purification, cleaning, compression, cooling, liquefaction and distillation which separates the air into the gases oxygen, nitrogen and argon.

Area

Part of premises that is specific to the manufacture of medicinal gases.

Blowing down

Blow the pressure down to atmospheric pressure.

Bulk gas

Any gas intended for medicinal use, which has completed all processing up to but not including final packaging.

Compressed gas

A gas which when packaged under pressure is entirely gaseous at -500 °C. (ISO 10286).

Container

A container is a cryogenic vessel, a tank, a tanker, a cylinder, a cylinder bundle or any other package that is in direct contact with the medicinal gas.

Cryogenic gas

Gas which liquefies at 1,013 bar at temperature below -1 500 °C.

Cryogenic vessel

A static or mobile thermally insulated container designed to contain liquefied or cryogenic gases. The gas is removed in gaseous or liquid form.

Cylinder

A transportable, pressure container with a water capacity not exceeding 150 litres. In this document when using the word cylinder it includes cylinder bundle (or cylinder pack) when appropriate.

Cylinder bundle

An assembly of cylinders, which are fastened together in a frame and interconnected by a manifold, transported and used as a unit.

Evacuate

To remove the residual gas in a container by pulling a vacuum on it.

Gas

A substance or a mixture of substances that is completely gaseous at 1,013 bar (101,325 kPa) and +150 °C or has a vapour pressure exceeding 3 bar (300 kPa) at +500 °C. (ISO 10286).

Hydrostatic pressure test

Test performed for safety reasons as required by national or international guideline in order to make sure that cylinders or tanks can withhold high pressures.

Liquefied gas

A gas which when packaged under pressure, is partially liquid (gas over a liquid) at -500 °C.

GLOSSARY *continued*

Manifold

Equipment or apparatus designed to enable one or more gas containers to be emptied and filled at a time.

Maximum theoretical residual impurity

Gaseous impurity coming from a possible repollution and remaining after the cylinders pre-treatment before filling. The calculation of the maximum theoretical impurity is only relevant for compressed gases and supposes that these gases act as perfect gases.

Medicinal gas

Any gas or mixture of gases intended to be administered to patients for therapeutic, diagnostic or prophylactic purposes using pharmacological action and classified as a medicinal product.

Minimum pressure retention valve

Valve equipped with a non-return system which maintains a definite pressure (about 3 to 5 bars over atmospheric pressure) in order to prevent contamination during use.

Non-return valve

Valve which permits flow in one direction only.

Purge

To empty and clean a cylinder
by blowing down and evacuating or
by blowing down, partial pressurisation with the gas in question and then blowing down.

Tank

Static container for the storage of liquefied or cryogenic gas.

Tanker

Container fixed on a vehicle for the transport of liquefied or cryogenic gas.

Valve

Device for opening and closing containers.

ANNEX 7

MANUFACTURE OF HERBAL MEDICINAL PRODUCTS

7.1 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 (**Note:** *Throughout the annex and unless otherwise specified, the term “herbal medicinal product / preparation” includes “complementary herbal medicinal product / preparation”*), can be a medicinal plant, an herbal substance (**Note:** *The terms herbal substance and herbal preparation are considered to be equivalent to the terms herbal drug and herbal drug preparation respectively or an herbal preparation*).

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 national or international guidance document(s) such as the “Guideline on Good Agricultural and Collection Practice for starting materials of herbal origin”.

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

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 Note

The GMP classification of the herbal material is dependent upon the use made of it by the Applicant/ Holder of Certificate of Registration (HCR). The material may be classified as an active substance, an intermediate or a finished product. It is the responsibility of the Applicant 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.*

7.1 PRINCIPLE *continued*

*** 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 MCC may in future carry out GMP inspections of these activities in order to assess compliance.*

7.2 PREMISES

7.2.1 Storage areas

7.2.1.1 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, prevent fermentation or mould growth and to prevent cross-contamination.

7.2.1.2 Different enclosed areas should be used to quarantine incoming herbal substances and for the approved herbal substances.

7.2.1.3 The storage area should be well aerated and the containers should be located in such a way as to allow free circulation of air.

7.2.1.4 Special attention should be paid to the cleanliness and good maintenance of the storage areas particularly when dust is generated.

7.2.1.5 Storage of herbal substances and herbal preparations may require special conditions of humidity, temperature or light protection; these conditions should be provided and monitored.

7.2.2 Production area

Specific provisions should be taken 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.

7.2.3 Equipment

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.

7.3 DOCUMENTATION

7.3.1 Specifications for starting materials

7.3.1.1 Herbal medicinal product manufacturers must ensure that they use only herbal starting materials manufactured in accordance with GMP and the Marketing Authorisation/Registration dossier. Comprehensive documentation on audits of the herbal starting material suppliers carried out by, or on behalf of the herbal medicinal product manufacturer should be made available. Audit trails for the active substance are fundamental to the quality of the starting material. The manufacturer should ensure that the suppliers of the herbal substance / preparation are in compliance with Good Agricultural and Collection Practice.

7.3.1.2 To fulfil the specification requirements described in the basic requirements of the general Guide to GMP (Chapter 4) documentation for herbal substances / preparations should include:

7.3.1 Specifications for starting materials – continued

- (i) 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;
- (ii) 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.);
- (iii) which part(s) of the plant is/are used;
- (iv) when a dried plant is used, the drying system should be specified;
- (v) a description of the herbal substance and its macro and/or microscopical examination;
- (vi) 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;
- (vii) assay of constituents of known therapeutic activity or where appropriate of markers; the methods suitable to determine possible pesticide contamination and limits accepted in accordance with the relevant Pharmacopoeia methods or, in absence of thereof, with an appropriate validated method, unless otherwise justified;
- (viii) tests to determine fungal and/or microbial contamination, including aflatoxins, other mycotoxins, pest-infestations, and limits accepted as appropriate;
- (ix) tests for toxic metals and for likely contaminants and adulterants, as appropriate;
- (x) tests for foreign materials as appropriate;
- (xi) the water content for herbal substances, determined in accordance with the relevant Pharmacopoeia;
- (xii) 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.

7.3.1.2 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.

7.3.2 Processing instructions

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 sizes or particle size.

For the production of a herbal preparation, instructions should include details of solvent, time and temperatures of extraction, details of any concentration stages and methods used.

7.4 QUALITY CONTROL**7.4.1 Sampling**

7.5.1 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.

7.5.2 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.

7.4.1 Sampling - continued

- 7.5.3 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 recognize adulteration, the presence of fungal growth, infestations, non-uniformity within a delivery of crude plants, etc.

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 complementary medicinal products and, where relevant to specific Pharmacopoeial Monographs.

ANNEX 8**SAMPLING OF STARTING AND PACKAGING MATERIALS****8.1 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 this Guide to GMP, items 6.5.1 to 6.5.4. This Annex gives additional guidance on the sampling of starting and packaging materials.

8.2 PERSONNEL

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.

8.3 STARTING MATERIALS

8.3.1 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.

8.3.2 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).

8.3 **STARTING MATERIALS** *continued*

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.

8.3.3 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.

8.4 **PACKAGING MATERIAL**

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 9**MANUFACTURE OF LIQUIDS, CREAMS AND OINTMENTS****9.1 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 this SA Guide to GMP and with the other supplementary Annexes, where applicable. This Annex only stresses points which are specific to this manufacture.

9.2 PREMISES AND EQUIPMENT

9.2.1 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.

9.2.2 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.

9.2.3 The use of glass apparatus should be avoided wherever possible.

High quality stainless steel is often the material of choice for product contact parts.

9.3 PRODUCTION

9.3.1 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.

9.3.2 The quality of materials received in bulk tankers should be checked before they are transferred to bulk storage tanks.

9.3.3 Care should be taken when transferring materials via pipelines to ensure that they are delivered to their correct destination.

9.3.4 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.

9.3.5 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.

9.3.6 When the finished product is not immediately packaged, the maximum period of storage and the storage conditions should be specified and respected.

ANNEX 10**MANUFACTURE OF PRESSURISED METERED DOSE AEROSOL PREPARATIONS FOR INHALATION****10.1 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 this SA Guide to GMP and with the other supplementary Annexes, where applicable. This Annex only stresses points which are specific to this manufacture.

10.2 GENERAL

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.

10.3 PREMISES AND EQUIPMENT

10.3.1 Manufacture and filling should be carried out as far as possible in a closed system.

10.3.2 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.

10.4 PRODUCTION AND QUALITY CONTROL

10.4.1 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.

10.4.2 All fluids (e.g. liquid or gaseous propellants) should be filtered to remove particles greater than 0,2 µm. An additional filtration where possible immediately before filling is desirable.

10.4.3 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.

10.4 PRODUCTION AND QUALITY CONTROL *continued*

- 10.4.4 Precautions should be taken to ensure uniformity of suspensions at the point of fill throughout the filling process.
- 10.4.5 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.
- 10.4.6 Controls after filling should ensure the absence of undue leakage. Any leakage test should be performed in a way which avoids microbial contamination or residual moisture.

ANNEX 11**COMPUTERISED SYSTEMS****11.1 PRINCIPLE**

The introduction of computerised systems into systems of manufacturing, including storage, distribution and quality control does not alter the need to observe the relevant principles given elsewhere in the Guide.

Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality or quality assurance.

Consideration should be given to the risk of losing aspects of the previous system by reducing the involvement of operators.

11.2 PERSONNEL

It is essential that there is the closest co-operation between key personnel and those involved with computer systems. Persons in responsible positions should have the appropriate training for the management and use of systems within their field of responsibility which utilises computers. This should include ensuring that appropriate expertise is available and used to provide advice on aspects of design, validation, installation and operation of computerised system.

11.3 VALIDATION

The extent of validation necessary will depend on a number of factors including the use to which the system is to be put, whether it is prospective or retrospective and whether or not novel elements are incorporated.

Validation should be considered as part of the complete life cycle of a computer system. This cycle includes the stages of planning, specification, programming, testing, commissioning, documentation, operation, monitoring and changing.

11.4 SYSTEM

11.4.1 Attention should be paid to the siting of equipment in suitable conditions where extraneous factors cannot interfere with the system.

11.4.2 A written detailed description of the system should be produced (including diagrams as appropriate) and kept up to date.

It should describe the principles, objectives, security measures and scope of the system and the main features of the way in which the computer is used and how it interacts with other systems and procedures.

11.4.3 The software is a critical component of a computerised system. The user of such software should take all reasonable steps to ensure that it has been produced in accordance with a system of Quality Assurance.

11.4.4 The system should include, where appropriate, built-in checks of the correct entry and processing of data.

11.4.5 Before a system using a computer is brought into use, it should be thoroughly tested and confirmed as being capable of achieving the desired results.

If a manual system is being replaced, the two should be run in parallel for a time, as part of this testing and validation.

11.4 SYSTEM continued

- 11.4.6 Data should only be entered or amended by persons authorised to do so.
Suitable methods of deterring unauthorised entry of data include the use of keys, pass cards, personal codes and restricted access to computer terminals.
There should be a defined procedure for the issue, cancellation, and alteration of authorization to enter and amend data, including the changing of personal passwords.
Consideration should be given to systems allowing for recording of attempts to access by unauthorised persons.
- 11.4.7 When critical data are being entered manually (for example the weight and batch number of an ingredient during dispensing), there should be an additional check on the accuracy of the record which is made. This check may be done by a second operator or by validated electronic means.
- 11.4.8 The system should record the identity of operators entering or confirming critical data.
Authority to amend entered data should be restricted to nominated persons.
Any alteration to an entry of critical data should be authorised and recorded with the reason for the change.
Consideration should be given to the system creating a complete record of all entries and amendments (an "audit trail").
- 11.4.9 Alterations to a system or to a computer program should only be made in accordance with a defined procedure which should include provision for validating, checking, approving and implementing the change.
Such an alteration should only be implemented with the agreement of the person responsible for the part of the system concerned, and the alteration should be recorded.
Every significant modification should be validated.
- 11.4.10 For quality auditing purposes, it shall be possible to obtain meaningful printed copies of electronically stored data.
- 11.4.11 Data should be secured by physical or electronic means against wilful or accidental damage, and this in accordance with Chapter 4 item 4.2.12 of the Guide.
Stored data should be checked for accessibility, durability and accuracy.
If changes are proposed to the computer equipment or its programs, the above mentioned checks should be performed at a frequency appropriate to the storage medium being used.
- 11.4.12 Data should be protected by backing-up at regular intervals. Back-up data should be stored as long as necessary at a separate and secure location.
- 11.4.13 There should be available adequate alternative arrangements for systems which need to be operated in the event of a breakdown.
The time required to bring the alternative arrangements into use should be related to the possible urgency of the need to use them. For example, information required to effect a recall must be available at short notice.
- 11.4.14 The procedures to be followed if the system fails or breaks down should be defined and validated.
Any failures and remedial action taken should be recorded.
- 11.4.15 A procedure should be established to record and analyse errors and to enable corrective action to be taken.
- 11.4.16 When outside agencies are used to provide a computer service, there should be a formal agreement including a clear statement of the responsibilities of that outside agency (see Chapter 7).
- 11.4.17 When the release of batches for sale or supply is carried out using a computerised system, the system should recognise that only an Authorised Person can release the batches and it should clearly identify and record the person releasing the batches.

ANNEX 12**USE OF IONISING RADIATION IN THE MANUFACTURE OF MEDICINAL PRODUCTS****12.1 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.

12.2 RESPONSIBILITIES

12.2.1 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 licence.

12.2.2 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).

12.2.3 The required dose including justified limits will be stated in the medicine registration dossier for the product.

12.3 DOSIMETRY

12.3.1 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.

12.3.2 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.

12.3.3 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.

12.3.4 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.

12.3.5 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.

12.4 VALIDATION OF THE PROCESS

- 12.4.1 Validation is the action of proving that the process, i.e. the delivery of the intended absorbed dose to the product, will achieve the expected results. The requirements for validation are given more fully in the note for guidance on "the use of ionising radiation in the manufacture of medicinal products".
- 12.4.2 Validation should include dose mapping to establish the distribution of absorbed dose within the irradiation container when packed with product in a defined configuration.
- 12.4.3 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.

12.5 COMMISSIONING OF THE PLANT

12.5.1 General

- 12.5.1.1 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.
- 12.5.1.2 Commissioning should include the following elements:
- a) Design;
 - b) Dose mapping;
 - c) Documentation;
 - d) Requirement for re-commissioning.

12.5.2 Gamma irradiators

A Design

- 12.5.2.1 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.

12.5.2 Gamma irradiators A Design continued

- 12.5.2.2 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.
- 12.5.2.3 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.

B Dose Mapping

- 12.5.2.4 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.
- 12.5.2.5 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.
- 12.5.2.6 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.
- 12.5.2.7 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.
- 12.5.2.8 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.
- 12.5.2.9 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.

12.5.3 Electron Beam Irradiators**A Design**

- 12.5.3.1 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.
- 12.5.3.2 Key parameters controlled by the operator are the characteristics of the beam and the conveyor speed.

B Dose Mapping

12.5.3.3 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 12.5.2.5 to 12.2.5.8 .

12.5.3.4 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.

12.5.4 Re-commissioning

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.

12.6 PREMISES

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.

12.7 PROCESSING

12.7.1 Irradiation containers should be packed in accordance with the specified loading pattern(s) established during validation.

12.7.2 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.

12.7.3 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.

12.7.4 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.

12.7.5 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 medicine registration and occur within a predetermined time period.

Unplanned interruptions during irradiation should be notified to the holder of the medicine registration if this extends the irradiation process beyond a previously agreed period.

12.7.6 Non-irradiated products must be segregated from irradiated products at all times. Methods or doing this include the use of radiation indicators (12.7.3) and appropriate design of premises (12.6).

Gamma irradiators

- 12.7.7 For continuous processing modes, dosimeters should be placed so that at least two are exposed in the irradiation at all times.
- 12.7.8 For batch modes, at least two dosimeters should be exposed in positions related to the minimum dose position.
- 12.7.9 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.
- 12.7.10 For batch process modes source movement and exposure times for each batch should be monitored and recorded.
- 12.7.11 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

- 12.7.12 A dosimeter should be placed on every container.
- 12.7.13 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.

12.8 DOCUMENTATION

- 12.8.1 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.
- 12.8.2 The irradiation plant operator should certify in writing the range of doses received by each irradiated container within a batch or delivery.
- 12.8.3 Process and control records for each irradiation batch should be checked and signed by a nominated responsible person and retained. The method and place of retention should be agreed between the plant operator and the holder of the medicine registration.
- 12.8.4 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.

12.9 MICROBIOLOGICAL MONITORING

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 medicine registration dossier.

ANNEX 13

MANUFACTURE OF INVESTIGATIONAL MEDICINAL PRODUCTS

13.1 PRINCIPLE

- 13.1.1 Investigational medicinal products should be produced in accordance with the principles and the detailed guidelines of SA Guide to GMP. Other guidelines should be taken into account where relevant and as appropriate to the stage of development of the product.
- 13.1.2 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.
- 13.1.3 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.

- 13.1.4 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.

- 13.1.5 These challenges require personnel with a thorough understanding of, and training in, the application of GMP to investigational medicinal products. Cooperation is required with trial sponsors who undertake the ultimate responsibility for all aspects of the clinical trial including the quality of investigational medicinal products.
- 13.1.6 The increased complexity in manufacturing operations requires a highly effective quality system.

This Annex also includes guidance on ordering, shipping, and returning clinical supplies, which are at the interface with, and complementary to, guidelines on Good Clinical Practice.

Note

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 medicine registration and whether they have been repackaged. The advice and involvement of an Authorised Person is recommended in this task.

GLOSSARY

Blinding

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s).

Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

In relation to an investigational medicinal product, blinding shall mean the deliberate disguising of the identity of the product in accordance with the instructions of the sponsor.

Unblinding shall mean the disclosure of the identity of blinded products.

Clinical trial

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of one or more investigational medicinal product(s) with the object of ascertaining its/their safety and/or efficacy.

Comparator product

An investigational or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial.

Investigational medicinal product

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

Immediate packaging

The container or other form of packaging immediately in contact with the medicinal or investigational medicinal product.

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 permit and / or licence to manufacture / import.

Order

Instruction to process, package and/or ship a certain number of units of investigational medicinal product(s).

Outer packaging

The packaging into which the immediate container is placed.

GLOSSARY *continued***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 randomization 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.

13.2 QUALITY MANAGEMENT

- 13.2.1 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.
- 13.2.2 The product specifications and manufacturing instructions may be changed during development but full control and traceability of the changes should be maintained.

13.3 PERSONNEL

- 13.3.1 All personnel involved with investigational medicinal products should be appropriately trained in the requirements specific to these types of product.
- 13.3.2 The Authorised Person should in particular be responsible for ensuring that there are systems in place that meet the requirements of this Annexure and should therefore have a broad knowledge of pharmaceutical development and clinical trial processes. Guidance for the Authorised Person in connection with the certification of investigational medicinal products is given in paragraphs 13.8.1 to 13.8.4 .

13.4 PREMISES AND EQUIPMENT

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.

13.5 DOCUMENTATION

13.5.1 Specifications and instructions

13.5.1.1 Specifications (for starting materials, primary packaging materials, intermediate, bulk products and finished products), manufacturing formulations 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.

13.5.1.2 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.

13.5.2 Order

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.

13.5.3 Product specification file

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 Authorised Person and should therefore be accessible to him/her.

Where different manufacturing steps are carried out at different locations under the responsibility of different Authorised Persons, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations.

13.5.4 Manufacturing Formulations and Processing Instructions

13.5.4.1 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 Formulations 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.

13.5.4 Manufacturing Formulations and Processing Instructions continued

- 13.5.4.2 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.

13.5.5 Packaging Instructions

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.

13.5.6 Processing, testing and packaging batch records

- 13.5.6.1 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.
- 13.5.6.2 Batch manufacturing records should be retained at least for the periods specified in relevant regulations³.

13.6 PRODUCTION**13.6.1 Packaging materials**

Specifications and quality control checks should include measures to guard against unintentional unblinding due to changes in appearance between different batches of packaging materials.

13.6.2 Manufacturing operations

- 13.6.2.1 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.
- 13.6.2.2 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 validated.
- For sterile products, the validation of sterilising processes should be of the same standard as for products authorized 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.
- 13.6.2.3 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.

³ Refer to SA Guide to GCP

13.6.3 Principles applicable to comparator product

- 13.6.3.1 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.
- 13.6.3.2 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.

13.6.4 Blinding operations

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.

13.6.5 Randomisation code

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.

13.6.6 Packaging

- 13.6.6.1 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.
- 13.6.6.2 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.
- 13.6.6.3 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.

13.6.7 Labelling

- 13.6.7.1 Table 1 summarises the contents of items 13.6.7.1 to 13.6.7.5 that follow.
The following information should be included on labels, unless its absence can be justified, e.g. use of a centralised electronic randomisation system:
- a) name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding);
 - b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency;
 - c) the batch and/or code number to identify the contents and packaging operation;
 - d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;

13.6.7 Labelling continued

- 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.

13.6.7.2 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.

13.6.7.3 Particulars should appear in at least one of the official languages. The particulars listed in item 13.6.7.1 should appear on the immediate container and on the outer packaging (except for immediate containers in the cases described in items 13.6.7.4 & 13.6.7.5).

The requirements with respect to the contents of the label on the immediate container and outer packaging are summarised in table 1.

13.6.7.4 When the product is to be provided to the trial subject or the person administering the medication within an immediate container together with outer packaging that is intended to remain together, and the outer packaging carries the particulars listed in item 13.6.7.1 the following information shall be included on the label of the immediate container (or any sealed dosing device that contains the immediate container):

- 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.

13.6.7.5 If the immediate container takes the form of blister packs or small units such as ampoules on which the particulars required in item 13.6.7.1 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;

13.6.7.6 Symbols or pictograms may be included to clarify certain information mentioned above. Additional information, warnings and/or handling instructions may be displayed.

13.6.7 Labelling continued

13.6.7.7 If the planning of the trial does not require particular manufacturing or packaging processes, and the trial is conducted with registered products and the patients participating in the trial have the same characteristics as those covered by the registered indication, the following particulars should be added to the original container but should not obscure the original labelling:

- a) name of sponsor, contract research organisation or investigator;
- b) trial reference code allowing identification of the trial site, investigator and trial subject.

13.6.7.8 If it becomes necessary to change the use-by date, an additional label should be affixed to the investigational medicinal product.

This additional label should state the new use-by date and repeat the batch number.

It may be superimposed on the old use-by date, but for quality control reasons, not on the original batch number.

This operation should be performed at an appropriately authorised manufacturing site. However, when justified, it may be performed at the investigational site by or under the supervision of the clinical trial site pharmacist, or other health care professional in accordance with national regulations. Where this is not possible, it may be performed by the clinical trial monitor(s) who should be appropriately trained.

The operation should be performed in accordance with GMP principles, specific and standard operating procedures and under contract, if applicable, and should be checked by a second person.

This additional labelling should be properly documented in both the trial documentation and in the batch records.

13.7 QUALITY CONTROL

13.7.1 As processes may not be standardised or fully validated, testing takes on more importance in ensuring that each batch meets its specification.

13.7.2 Quality control should be performed in accordance with the Product Specification File and in accordance with the required information⁴. Verification of the effectiveness of blinding should be performed and recorded.

13.7.3 Samples of each batch of investigational medicinal product, including blinded product should be retained for the required periods⁵.

13.7.4 Consideration should be given to retaining samples from each packaging run/trial period 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.

13.8 RELEASE OF BATCHES

13.8.1 Release of investigational medicinal products (see item 13.9.1) should not occur until after the Authorised Person has certified that the relevant requirements have been met (see item 13.8.2). The Authorised Person should take into account the elements listed in item 13.8.2 as appropriate.

13.8.2 Assessment of each batch for certification prior to release may include as appropriate:

- a) 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;

⁴ Refer to SA Guide to GCP

⁵ Refer to SA Guide to GCP

13.8 RELEASE OF BATCHES continued

- b) production conditions;
- c) the validation status of facilities, processes and methods;
- d) examination of finished packs;
- e) where relevant, the results of any analyses or tests performed after importation;
- f) stability reports;
- g) the source and verification of conditions of storage and shipment;
- h) audit reports concerning the quality system of the manufacturer;
- i) 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;
- j) where relevant, regulatory requirements for registration of a medicine, SA GMP standards applicable and any official verification of GMP compliance;
- k) all other factors of which the Authorised 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 registered or unregistered in South Africa and its phase of development.

The sponsor should ensure that the elements taken into account by the Authorised Person when certifying the batch are consistent with the required information⁶. See also item 13.9.2 .

- 13.8.3 Where investigational medicinal products are manufactured and packaged at different sites under the supervision of different Authorised Persons, recommendations⁷ should be followed as applicable.
- 13.8.4 Where permitted, packaging or labelling is carried out at the investigator site by, or under the supervision of a clinical trials pharmacist, or other licensed health care professional as allowed in those regulations, the Authorised Person is not required to certify the activity in question. The sponsor is nevertheless responsible for ensuring that the activity is adequately documented and carried out in accordance with the principles of GMP and should seek the advice of the Authorised Person in this regard.

13.9 SHIPPING

- 13.9.1 Shipping of investigational products should be conducted according to instructions given by or on behalf of the sponsor in the shipping order.
- 13.9.2 Investigational medicinal products should remain under the control of the Sponsor until after completion of a two-step release procedure: certification by the Authorised Person; and release following fulfilment of the relevant requirements⁸. The sponsor should ensure that these are consistent with the details actually considered by the Authorised Person. Both releases should be recorded and retained in the relevant trial files held by or on behalf of the sponsor.
- 13.9.3 De-coding arrangements should be available to the appropriate responsible personnel before investigational medicinal products are shipped to the investigator site.
- 13.9.4 A detailed inventory of the shipments made by the manufacturer or importer should be maintained. It should particularly mention the addressees' identification.

⁶ See SA Guide to GCP re Ethics and MCC approvals prior to commencement

⁷ See Annex 16 to the SA Guide to GMP

⁸ See SA Guide to GCP re Ethics and MCC approvals prior to commencement

13.9 SHIPPING continued

- 13.9.5 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 Authorised Person should be sought. The product should be returned to the manufacturer, or another authorised manufacturer for re-labelling, if necessary, and certification by a Authorised Person. Records should be retained and full traceability ensured.

13.10 COMPLAINTS

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 Authorised Person and those responsible for the relevant clinical trial in order to assess any potential impact on the trial, product development and on subjects.

13.11 RECALLS AND RETURNS**13.11.1 Recalls**

- 13.11.1.1 Procedures for retrieving investigational medicinal products and documenting this retrieval should be agreed by the sponsor, in collaboration with the manufacturer or importer where different.

The investigator and monitor need to understand their obligations under the retrieval procedure.

- 13.11.1.2 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.

13.11.2 Returns

- 13.11.2.1 Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in approved written procedures.

- 13.11.2.2 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.

13.12 DESTRUCTION

- 13.12.1 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.

- 13.12.2 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.

- 13.12.3 When destruction of investigational medicinal products takes place a dated certificate of, or receipt for destruction, should be provided to the sponsor. These documents should clearly identify, or allow traceability to, the batches and/or patient numbers involved and the actual quantities destroyed.

TABLE 1 - SUMMARY OF LABELLING DETAILS (13.6.7.1 to 13.6.7.5)

- a) name, address and telephone number of the sponsor, contract research organisation or investigator (the main contact for information on product, clinical trial and emergency unblinding);
- b) pharmaceutical dosage form, route of administration, quantity of dosage units, and in the case of open trials, the name/identifier and strength/potency
- c) the batch and/or code number to identify the contents and packaging operation;
- d) a trial reference code allowing identification of the trial, site, investigator and sponsor if not given elsewhere;
- e) the trial subject identification number / treatment number and where relevant, the visit number;
- f) the name of the investigator (if not included in (a) or (d));
- g) directions for use (reference may be made to a leaflet or other explanatory document intended for the trial subject or person administering the product
- h) “for clinical trial use only” or similar wording;
- i) the storage conditions;
- j) period of use (use-by date, expiry date or re-test date as applicable), in month/year format and in a manner that avoids any ambiguity
- k) “keep out of reach of children” except when the product is for use in trials where the product is not taken home by subject

GENERAL CASE

For both the outer packaging and immediate container (13.6.7.1)

Particulars

a¹ to k

IMMEDIATE CONTAINER

Where immediate container and outer packaging remain together throughout (13.6.7.4)⁵

a² b³ c d e

IMMEDIATE CONTAINER

Blisters or small packaging units (13.6.7.5)⁵

a² b^{3,4} c d e

¹ 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 (13.6.7.2).

² The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not be included.

³ Route of administration may be excluded for oral solid dose for.

⁴ The pharmaceutical dosage form and quantity of dosage units may be omitted.

⁵ When the outer packaging carries the particulars listed in 13.6.7.5

ANNEX 14

MANUFACTURE OF PRODUCTS DERIVED FROM HUMAN BLOOD OR HUMAN PLASMA

14.1 PRINCIPLE

For biological medicinal products derived from human blood or plasma, starting materials include the source materials such as cells or fluids including blood or plasma.

Medicinal products derived from human blood or plasma have certain special features arising from the biological nature of the source material. For example, disease-transmitting agents, especially viruses, may contaminate the source material. The safety of these products relies therefore on the control of source materials and their origin as well as on the subsequent manufacturing procedures, including virus removal and inactivation.

The general chapters of the guide to GMP apply to medicinal products derived from human blood or plasma, unless otherwise stated. Some of the Annexes may also apply, e.g. manufacture of sterile medicinal products, use of ionizing radiation in the manufacture of medicinal products, manufacture of biological medicinal products and computerised systems.

Since the quality of the final products is affected by all the steps in their manufacture, including the collection of blood or plasma, all operations should therefore be done in accordance with an appropriate system of Quality Assurance and current Good Manufacturing Practice.

Necessary measures shall be taken to prevent the transmission of infectious diseases and the requirements and standards of the European, British or United States Pharmacopoeia monographs regarding plasma for fractionation and medicinal products derived from human blood or plasma shall be applicable. These measures shall also comprise other relevant guidelines such as the Council of Europe Recommendation of 29 June 1998 "On the suitability of blood and plasma donors and the screening of donated blood in the European Community"⁹ (98/463/EC), the recommendations of the Council of Europe (see "Guide to the preparation, use and quality assurance of blood components", Council of Europe Press) and the World Health Organisation (see report by the WHO Expert Committee on Biological Standardisation, WHO Technical Report Series 840, 1994).

Furthermore, the guidelines adopted by the CPMP, in particular "Note for guidance on plasma-derived medicinal products (CPMP/BWP/269/95rev.2)", "Virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses" published in Volume 3A of the series "The rules governing medicinal products in the European Community" may be helpful.

These documents are regularly revised and reference should be made to the latest revisions for current guidance.

The provisions of this annex apply to medicinal products derived from human blood and plasma. They do not cover blood components used in transfusion medicine. However many of these provisions may be applicable to such components and the Medicines Control Council may require compliance with them.

GLOSSARY

Blood:	Whole blood collected from a single donor and processed either for transfusion or further Manufacturing
Blood components:	Therapeutic components of blood (red cells, white cells, plasma, platelets), that can be prepared by centrifugation, filtration and freezing using conventional blood bank methodology
Medicinal product derived	Medicinal products based on blood constituents which from blood or plasma: are prepared industrially by public or private establishments

⁹ O.J. L 20321.7.1998 p.14

14.2 QUALITY MANAGEMENT

- 14.2.1 Quality Assurance should cover all stages leading to the finished product, from collection (including donor selection, blood bags, anticoagulant solutions and test kits) to storage, transport, processing, quality control and delivery of the finished product, all in accordance with the texts referred to under Principle at the beginning of this Annex.
- 14.2.2 Blood or plasma used as a source material for the manufacture of medicinal products should be collected by establishments and be tested in laboratories which are subject to inspection and approved by the Medicines Control Council.
- 14.2.3 Procedures to determine the suitability of individuals to donate blood and plasma, used as a source material for the manufacture of medicinal products, and the results of the testing of their donations should be documented by the collection establishment and should be available to the manufacturer of the medicinal product.
- 14.2.4 Monitoring of the quality of medicinal products derived from human blood or plasma should be carried out in such a way that any deviations from the quality specifications can be detected.
- 14.2.5 Medicinal products derived from human blood or plasma which have been returned unused should normally not be re-issued; (see also Chapter 5 item 5.10.5 of the main GMP guide).

14.3 PREMISES AND EQUIPMENT

- 14.3.1 The premises used for the collection of blood or plasma should be of suitable size, construction and location to facilitate their proper operation, cleaning and maintenance. Collection, processing and testing of blood and plasma should not be performed in the same area. There should be suitable donor interview facilities so that these interviews are carried out in private.
- 14.3.2 Manufacturing, collection and testing equipment should be designed, qualified and maintained to suit its intended purpose and should not present any hazard. Regular maintenance and calibration should be carried out and documented according to established procedures.
- 14.3.3 In the preparation of plasma-derived medicinal products, 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 treated products.

14.4 BLOOD AND PLASMA COLLECTION

- 14.4.1 A standard contract is required between the manufacturer of the medicinal product derived from human blood or plasma and the blood/plasma collection establishment or organisation responsible for collection.
- 14.4.2 Each donor must be positively identified at reception and again before venepuncture.
- 14.4.3 The method used to disinfect the skin of the donor should be clearly defined and shown to be effective. Adherence to that method should then be maintained.
- 14.4.4 Donation number labels must be re-checked independently to ensure that those on blood packs, sample tubes and donation records are identical.
- 14.4.5 Blood bag and apheresis systems should be inspected for damage or contamination before being used to collect blood or plasma. In order to ensure traceability, the batch number of blood bags and apheresis systems should be recorded.

14.5 TRACEABILITY AND POST COLLECTION MEASURES

- 14.5.1 While fully respecting confidentiality, there must be a system in place which enables the path taken by each donation to be traced, both forward from the donor and back from the finished medicinal product, including the customer (hospital or health care professional). It is normally the responsibility of this customer to identify the recipient.

14.5 TRACEABILITY AND POST COLLECTION MEASURES continued**14.5.2 Post-collection measures:**

A standard operating procedure describing the mutual information system between the blood/plasma collection establishment and the manufacturing/fractionation facility should be set up so that they can 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/ infusion infection which implicates or can be traced back to the donor.

The procedures to be followed in the event of any of the above should be documented in the standard operating procedure.

Look-back should consist of tracing back of previous donations for at least six months prior to the last negative donation.

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.

Where there are indications that a donation contributing to a plasma pool was infected with HIV or hepatitis A, B or C, the case should be referred to the Medicines Control Council and the company's view regarding continued manufacture from the implicated pool or of the possibility of withdrawal of the product(s) should be given.

14.6 PRODUCTION AND QUALITY CONTROL

14.6.1 Before any blood and plasma donations, or any product derived therefrom are released for issue and/or fractionation, they should be tested, using a validated test method of suitable sensitivity and specificity, for the following markers of specific disease-transmitting agents:

- HBsAg;
- Antibodies to HIV 1 and HIV 2;
- Antibodies to HCV.

If a repeat-reactive result is found in any of these tests, the donation is not acceptable. (Additional tests may form part of Department of Health requirements.)

14.6.2 The specified storage temperatures of blood, plasma and intermediate products when stored and during transportation from collection establishments to manufacturers, or between different manufacturing sites, should be checked and validated. The same applies to delivery of these products.

14.6.3 The first homogeneous plasma pool (e.g. after separation of the cryoprecipitate) should be tested using a validated test method, of suitable sensitivity and specificity, and found non-reactive for the following markers of specific disease-transmitting agents:

- HBsAg;
- Antibodies to HIV 1 and HIV 2;
- Antibodies to HCV.

Confirmed positive pools must be rejected.

14.6 PRODUCTION AND QUALITY CONTROL continued

- 14.6.4 Only batches derived from plasma pools tested and found non-reactive for HCV RNA by nucleic acid amplification technology (NAT), using a validated test method of suitable sensitivity and specificity, should be released.
- 14.6.5 Testing requirements for viruses, or other infectious agents, should be considered in the light of knowledge emerging as to infectious agents and the availability of appropriate test methods.
- 14.6.6 The labels on single units of plasma stored for pooling and fractionation must comply with the provisions of the European, British or United States Pharmacopoeia monograph "Human plasma for fractionation" and bear at least the identification number of the donation, the name and address of the collection establishment or the references of the blood transfusion service responsible for preparation, the batch number of the container, the storage temperature, the total volume or weight of plasma, the type of anticoagulant used and the date of collection and/or separation.
- 14.6.7 In order to minimise the microbiological contamination of plasma for fractionation or the introduction of foreign material, the thawing and pooling should be performed at least in a grade D clean area, wearing the appropriate clothing and in addition face masks and gloves should be worn. Methods used for opening bags, pooling and thawing should be regularly monitored, e.g. by testing for bioburden. The cleanroom requirements for all other open manipulations should conform to the requirements of Annex 1 of this SA Guide to GMP.
- 14.6.8 Methods for clearly distinguishing between products or intermediates which have undergone a process of virus removal or inactivation, from those which have not, should be in place.
- 14.6.9 Validation of methods used for virus removal or virus inactivation should not be conducted in the production facilities in order not to put the routine manufacture at any risk of contamination with the viruses used for validation.

14.7 RETENTION OF SAMPLES

Where possible, samples of individual donations should be stored to facilitate any necessary look-back procedure. This would normally be the responsibility of the collection establishment. Samples of each pool of plasma should be stored under suitable conditions for at least one year after the expiry date of the finished product with the longest shelf-life.

14.8 DISPOSAL OF REJECTED BLOOD, PLASMA OR INTERMEDIATES

There should be a standard operating procedure for the safe and effective disposal of blood, plasma or intermediates.

ANNEX 15**QUALIFICATION AND VALIDATION****15.1 PRINCIPLE**

This Annexure describes the principles of qualification and validation which are applicable to the manufacture of medicinal products.

It is a requirement of GMP that manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations.

Significant changes to the facilities, the equipment and the processes, which may affect the quality of the product, should be validated.

A risk assessment approach should be used to determine the scope and extent of validation.

15.2 PLANNING FOR VALIDATION

15.2.1 All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents.

15.2.2 The VMP should be a summary document which is brief, concise and clear.

15.2.3 The VMP should contain data on at least the following:

- validation policy;
- organisational structure of validation activities;
- summary of facilities, systems, equipment and processes to be validated;
- documentation format: the format to be used for protocols and reports;
- planning and scheduling;
- change control;
- reference to existing documents.

15.2.4 In case of large projects, it may be necessary to create separate validation master plans.

15.3 DOCUMENTATION

15.3.1 A written protocol should be established that specifies how qualification and validation will be conducted.

The protocol should be reviewed and approved.

The protocol should specify critical steps and acceptance criteria.

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

Any changes to the plan as defined in the protocol should be documented with appropriate justification.

15.3.3 After completion of a satisfactory qualification, a formal release for the next step in qualification and validation should be made as a written authorisation.

15.4 QUALIFICATION

15.4.1 Design qualification

- 15.4.1.1 The first element of the validation of new facilities, systems or equipment could be design qualification (DQ).
- 15.4.1.2 The compliance of the design with GMP should be demonstrated and documented.

15.4.2 Installation qualification

- 15.4.2.1 Installation qualification (IQ) should be performed on new or modified facilities, systems and equipment.
- 15.4.2.2 IQ should include, but not be limited to the following:
 - a) installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;
 - b) collection and collation of supplier operating and working instructions and maintenance requirements;
 - c) calibration requirements;
 - d) verification of materials of construction.

15.4.3 Operational qualification

- 15.4.3.1 Operational qualification (OQ) should follow Installation qualification.
- 15.4.3.2 OQ should include, but not be limited to the following:
 - a) tests that have been developed from knowledge of processes, systems and equipment;
 - b) tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as "worst case" conditions.
- 15.4.3.3 The completion of a successful Operational qualification should allow the finalisation of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal "release" of the facilities, systems and equipment.

15.4.4 Performance qualification

- 15.4.4.1 Performance qualification (PQ) should follow successful completion of Installation qualification and Operational qualification.
- 15.4.4.2 PQ should include, but not be limited to the following:
 - a) tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment;
 - b) tests to include a condition or set of conditions encompassing upper and lower operating limits.
- 15.4.4.3 Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ.

15.4.5 Qualification of established (in-use) facilities, systems and equipment

Evidence should be available to support and verify the operating parameters and limits for the critical variables of the operating equipment. Additionally, the calibration, cleaning, preventative maintenance, operating procedures and operator training procedures and records should be documented.

15.5 PROCESS VALIDATION

15.5.1 General

- 15.5.1.1 The requirements and principles outlined in this chapter are applicable to the manufacture of pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes and revalidation.
- 15.5.1.2 Process validation should normally be completed prior to the distribution and sale of the medicinal product (prospective validation). In exceptional circumstances, where this is not possible, it may be necessary to validate processes during routine production (concurrent validation). Processes in use for some time should also be validated (retrospective validation).
- 15.5.1.3 Facilities, systems and equipment to be used should have been qualified and analytical testing methods should be validated. Staff taking part in the validation work should have been appropriately trained.
- 15.5.1.4 Facilities, systems, equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner.

15.5.2 Prospective validation

- 15.5.2.1 Prospective validation should include, but not be limited to the following:
- short description of the process;
 - summary of the critical processing steps to be investigated;
 - list of the equipment/facilities to be used (including measuring / monitoring / recording equipment) together with its calibration status
 - finished product specifications for release;
 - list of analytical methods, as appropriate;
 - proposed in-process controls with acceptance criteria;
 - additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;
 - sampling plan;
 - methods for recording and evaluating results
 - functions and responsibilities;
 - proposed timetable.
- 15.5.2.2 Using this defined process (including specified components) a series of batches of the final product may be produced under routine conditions. In theory the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, would constitute a validation of the process.
- 15.5.2.3 Batches made for process validation should be the same size as the intended industrial scale batches.
- 15.5.2.4 If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise, and (where applicable) the marketing authorisation.

15.5.3 Concurrent validation

- 15.5.3.1 In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.
- 15.5.3.2 The decision to carry out concurrent validation must be justified, documented and approved by authorised personnel.
- 15.5.3.3 Documentation requirements for concurrent validation are the same as specified for prospective validation.

15.5.4 Retrospective validation

- 15.5.4.1 Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.
- 15.5.4.2 Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.
- 15.5.4.3 The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance log books, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results.
- 15.5.4.4 Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.
- 15.5.4.5 For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches may be examined if justified.

15.6 CLEANING VALIDATION

- 15.6.1 Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure. The rationale for selecting limits of carry over of product residues, cleaning agents and microbial contamination should be logically based on the materials involved. The limits should be achievable and verifiable.
- 15.6.2 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.
- 15.6.3 Normally only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to non-contact parts. The intervals between use and cleaning as well as cleaning and reuse should be validated. Cleaning intervals and methods should be determined.
- 15.6.4 For cleaning procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilising a "worst case" approach can be carried out which takes account of the critical issues.
- 15.6.5 Typically three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.
- 15.6.6 "Test until clean" is not considered an appropriate alternative to cleaning validation.
- 15.6.7 Products which simulate the physicochemical properties of the substances to be removed may exceptionally be used instead of the substances themselves, where such substances are either toxic or hazardous.

15.7 ANALYTICAL METHOD VALIDATION

- 15.7.1 Analytical testing procedures including stability testing methods must be validated to demonstrate their reliability. This should be done during product design.
- 15.7.2 Revalidation may be necessary in the following circumstances:
- changes in the synthesis of a drug substance;
 - changes in the composition of a finished product;
 - changes in the analytical procedure
 - changes in the manufacturing process that will effect the method

15.7 Analytical Method Validation continued

- 15.7.3 The degree of revalidation required depends on the nature of the changes. Certain other changes may also require validation.
- 15.7.4 Analytical method validation should not be confused with system suitability tests. System suitability testing verifies the suitability of an analytical system at the time the test is performed.
- 15.7.5 Analytical methods, (other than pharmacopoeial methods), should be validated. Typical validation characteristics which should be considered, include accuracy, precision, (repeatability and intermediate precision), specificity, detection limit, quantitation limit, linearity and range. Robustness should be considered at an appropriate stage in the development of an analytical procedure.
- 15.7.6 Reference may be made to: ICH Q2 Validation of Analytical Procedures: Text and Methodology <http://www.ich.org>

15.8 CHANGE CONTROL

- 15.8.1 Written procedures should be in place to describe the actions to be taken if a change is proposed to a starting material, product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or reproducibility of the process. Change control procedures should ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specifications.
- 15.8.2 All changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. The need for, and the extent of, requalification and re-validation should be determined.

15.9 REVALIDATION

Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation.

GLOSSARY

Definitions of terms relating to qualification and validation which are not given in the glossary of the current SA Guide to GMP, but which are used in this Annex, are given below.

Change Control

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state.

Cleaning Validation

Cleaning validation is documented evidence that an approved cleaning procedure will provide equipment which is suitable for processing medicinal products.

Concurrent Validation

Validation carried out during routine production of products intended for sale.

GLOSSARY continued

Design qualification (DQ)

The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.

Installation Qualification (IQ)

The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.

Operational Qualification (OQ)

The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.

Performance Qualification (PQ)

The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification.

Process Validation

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

Prospective Validation

Validation carried out before routine production of products intended for sale.

Retrospective Validation

Validation of a process for a product which has been marketed based upon accumulated manufacturing, testing and control batch data.

Re-Validation

A repeat of the process validation to provide an assurance that changes in the process/equipment introduced in accordance with change control procedures do not adversely affect process characteristics and product quality.

Risk analysis

Method to assess and characterise the critical parameters in the functionality of an equipment or process.

Simulated Product

A material that closely approximates the physical and, where practical, the chemical characteristics (e.g. viscosity, particle size, pH etc.) of the product under validation. In many cases, these characteristics may be satisfied by a placebo product batch.

System

A group of equipment with a common purpose.

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.

ANALYTICAL METHOD VALIDATION GLOSSARY

Analytical Procedure

The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to: the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.

Specificity

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc.

Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s).

This definition has the following implications:

Identification: to ensure the identity of an analyte.

Purity Tests: to ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, i.e. related substances test, heavy metals, residual solvents content, etc.

Assay (content or potency): to provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample.

Accuracy

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

This is sometimes termed trueness.

Precision

The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility.

Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample it may be investigated using artificially prepared samples or a sample solution.

The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements.

Repeatability

Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision.

Intermediate precision

Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc.

Reproducibility

Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).

Detection Limit

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

*Analytical Method Validation Glossary continued***Quantitation Limit**

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.

Linearity

The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

Range

The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity.

Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

ANNEX 16

ORGANISATION AND PERSONNEL

16.1 PRINCIPLES

The company must have an organisation chart. The organogram should clearly indicate the reporting lines and level of responsibility, and should be authorised and be in accordance with the functional relationships described in the individual job descriptions of the functionaries referred to.

The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of medicines rely upon people. For this reason, there should be sufficient personnel at all levels with the ability, training, experience and, where necessary, the professional / technical qualifications and managerial skills appropriate to the tasks assigned to them.

Their duties and responsibilities should be clearly explained to them and recorded as job descriptions. Proper job descriptions should include the responsibilities and document in detail the policy and requirements.

All personnel should be aware of the principles of Good Manufacturing Practice (GMP) that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

Responsibilities should be delegated and acceptance acknowledged in writing. 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 application of GMP.

The way in which the various key responsibilities which can influence product quality are allocated may vary with different manufacturers. These responsibilities should be clearly defined and delegated.

The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

Suitably qualified persons should be designated in writing to take up the duties of key personnel during the absence of the latter.

Key personnel should be provided with adequate supporting staff.

Persons in responsible positions should have sufficient authority to discharge their responsibilities. In particular, the person responsible for Quality Assurance should be able to carry out his defined functions impartially.

The person responsible for Production and the person responsible for Quality Assurance, should be different persons of equal level of authority, neither of whom should be responsible to the other, but who both have a responsibility for achieving the requisite quality.

The duties of this person responsible for Quality Assurance are wider than those which may be suggested by such terms as "Chief Analyst", "Laboratory Head", etc.

16.2 RESPONSIBILITIES OF KEY PERSONNEL

Key personnel include

- a natural person who resides in South Africa responsible to the Medicines Control Council for compliance with the requirements of the Medicines and Related Substances Act, 1965 (Act 101 of 1965).
- the person responsible for Production,
- the person responsible for Quality Assurance, and

16.2 **RESPONSIBILITIES OF KEY PERSONNEL** *continued*

- the Responsible Pharmacist responsible to the
 - Medicines Control Council for compliance with the requirements of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) and the
 - Pharmacy Council for compliance with the requirements of the Pharmacy Act, 1974 (Act 53 of 1974)

Head of Production

The Production Manager, in addition to his responsibilities (Chapter 2) for

- production areas, equipment, operations and records
- the management of production personnel; and for
- the manufacture of products in accordance with the appropriate Master Formulation and Manufacturing instructions,

will have other responsibilities bearing on quality, which he should share or exercise jointly with the person responsible for Quality Control.

Head of Quality Control

The person responsible for Quality Control should have the authority to establish, verify and implement all quality control procedures (Chapter 2).

In some companies the Quality Assurance Manager oversees all the quality assurance arrangements and reports to senior management. The person responsible for Quality Control may report to the Quality Assurance Manager and share some of the responsibilities with him.

The person responsible for Quality Assurance should be part of the decision-making process in all matters that affect the quality of products including development, production, laboratory, storage, distribution, vendors and third party contractors.

Shared or joint responsibilities of the Head of Production and Head of Quality Control (Chapter 2)

It is important that both direct and shared responsibilities are understood by those concerned.

The Responsible Pharmacist contemplated in regulation 25 (3) of the Pharmacy Act and the relevant sections of the Medicines Act must:

- ensure that he or she in fact continuously supervises the pharmacy in which he or she has been appointed
- have appropriate qualifications and experience in the services being rendered by such pharmacy
- ensure that persons being employed in such pharmacy and who provide services forming part of the scope of pharmacy practice of a pharmacist are appropriately registered with the Pharmacy Council
- notify the Pharmacy Council immediately upon receiving knowledge that his/her services as responsible pharmacist have been or will be terminated
- take corrective measures in respect of deficiencies with regard to inspection reports of the Pharmacy Council or in terms of the Medicines Act; and
- in addition to the general responsibilities also –
 - ensure that unauthorised persons do not obtain access to medicines or scheduled substances or the pharmacy premises outside of normal trading hours
 - establish policies and procedures for the employees of the pharmacy with regard to the acts performed and services provided in the pharmacy
 - ensure the safe and effective storage and keeping of medicine or scheduled substances in the pharmacy under his or her direct personal supervision;

The Responsible Pharmacist continued

- ensure correct and effective record keeping of the purchase, sale, possession, storage, safekeeping, and return of medicines or scheduled substances;
- initiate and co-ordinate all recall activities, which should involve the head of Quality Management;
- ensure that a letter of authorisation to communicate with Council, signed by the CEO, be submitted to the MCC;
- compile a letter of delegation of authority in her / his absence;
- control the manufacturing or distribution of medicines, scheduled substances or medical devices in terms of the provisions of the Medicines Act, 1965;
- ensure that there is compliance with Good Pharmacy Practice as published by the Pharmacy Council;
- be part of the decision making process affecting the pharmacy business;
- supervise every pharmacist appointed by the owner of a pharmacy business, if applicable
- ensure that the pharmacy owner complies with all the conditions of –
 - ownership of such pharmacy business
 - registration of the pharmacy
- ensure that no person is appointed to perform any act falling outside the scope of practice of the category in which such person is registered or which he/she is not authorised to perform in terms of the Pharmacy Act, 1974 (Act 53 of 1974);
- report in writing any non-compliance with the Pharmacy Act to the management of such pharmacy business and furnish Pharmacy Council with a copy thereof;
- not introduce or carry out any instruction or order of management with regard to the pharmacy business of the pharmacy owner which could amount to a contravention of legislation applicable to such pharmacy business; and
- be responsible to the Medicines Control Council for compliance with the provisions of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) relating to the sale, control of the manufacturing and distribution of medicines, scheduled substances or medical devices.

A Pharmacist or other legally authorised person is responsible for:

- independently checking and signing each dispensed material and its mass or volume;
- checking and signing the addition of each material to the mix;
- checking and signing the identity of the bulk product and printed packaging material;
- checking and signing that each packaging line or station is clear of previous product, packaging components records or materials not required for the planned packaging operations, and that equipment is clean and suitable for use before any packaging is undertaken. These checks should be recorded and each packaging line opened and closed by a pharmacist, other legally authorised person or quality control.
- the release for sale of the finished product. This release should include the completion of a check list which will ensure that all important release criteria have been met;
- handling scheduled substances in a pharmacy. Legal requirements regarding the documentation and control of scheduled medicines should be adhered to;
- dealing with complaints. A system should be established for dealing with complaints, which should include written procedures indicating the responsible person(s) (e.g. pharmacist) through whom the complaints are to be channelled. The responsible person must have appropriate knowledge and experience and the necessary authority to decide the action to be taken;
- dealing with adverse events. A system should be established for dealing with adverse events, which should include written procedures indicating the responsible person(s) (e.g. pharmacist) through whom the reports and activities are to be channelled. The responsible person must have appropriate knowledge and experience and the necessary authority to decide the action to be taken.

Consultants

Only in exceptional circumstances should persons engaged part time or in a consultative capacity be appointed to key positions. Consultants advising on the manufacture, processing, packing, or storage of medicines shall have sufficient education, training and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address and qualifications of any consultants and the type and period of service they provide.

16.3 LEGAL ASPECTS

16.3.1 DEFINITIONS

16.3.1.1 PHARMACY ACT (ACT 53 OF 1974) & REGULATIONS (Pharmacy Act)

Quoted for ease of reference – the original source takes precedence

“direct personal supervision” means guidance and support by a pharmacist whilst physically present in a pharmacy

“indirect personal supervision” means guidance and support by a pharmacist in accordance with a standard operating procedure approved by the Pharmacy Council whilst absent from the pharmacy.

“manufacture” means all operations including purchasing of raw material, processing, production, packaging, releasing, storage, quality assurance, importation, exportation of medicine and scheduled substances and related control.

“manufacturing pharmacy” means a pharmacy wherein or from which some or all of the services as prescribed in regulation 16 of the Pharmacy Act relating to the Practice of Pharmacy are provided and which shall sell medicine only to a wholesale pharmacy or a community pharmacy or an institutional pharmacy or to persons who are authorised to purchase medicines in terms of the Medicines Act or to an organ of State.

(Also refer to the regulations relating to the registration of persons and the maintenance of registers – GNR 1160 of 20 Nov. 2000)

“nominee” means the natural person appointed and registered as such by a company entitled to carry on the business of a pharmacist in terms of the Pharmacy Act and who shall be responsible for performing the duties as prescribed in regulation 24 of Pharmacy Act *(GNR 1160 of 20 Nov. 2000)*

“responsible pharmacist” means a natural person who is a pharmacist and who shall be responsible to the Pharmacy Council for complying with all the provisions of Pharmacy Act and other legislation applicable to services which specially pertain to the scope of practice of a pharmacist, and the legislation applicable to the pharmacy which is under his or her personal supervision and who is registered as such in terms of the Pharmacy Act.

16.3.1.2 MEDICINES AND RELATED SUBSTANCES ACT (ACT 101 OF 1965) & REGULATIONS (Medicines Act)

Quoted for ease of reference – the original source takes precedence

“manufacture” means all operations including purchasing of material, processing, production, packaging, releasing, storage and shipment of medicines and related substances in accordance with quality assurance and related controls

“medicine” means any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in –

- (a) the diagnosis, treatment, mitigation, modification, or prevention of disease, abnormal physical, or mental state or the symptoms thereof in man; or

16.3.1 DEFINITIONS cont.

- (b) restoring, correcting, or modifying any somatic or psychic or organic function in man,

and includes any veterinary medicine

“public” includes a section of the public concerned with manufacturing, dispensing, selling, or administering, or the issue of a prescription for medicines or a Scheduled substance

“responsible pharmacist” means a responsible pharmacist as defined in the Pharmacy Act, 1974

16.3.2 Pharmaceutical Companies

The Pharmacy Act sets certain requirements for pharmaceutical companies, the Responsible Pharmacist and pharmacists e.g.:

- the company and the Responsible Pharmacist (who must be residing in the Republic) must be registered with the Pharmacy Council
- pharmaceutical operations must be conducted under the personal supervision of a pharmacist whose name is displayed over the main entrance
- certain duties and responsibilities must be performed by pharmacists e.g. manipulation, preparation or compounding of medicines, manufacturing, and the furnishing of advice with regard to medicines, distribution and the sale of medicines.

The Medicines Act further sets requirements for the following activities:

- labelling of medicines, including package inserts
- records and registers for scheduled medicines
- sale of medicines only to registered and approved customers
- registration of medicines with the Medicines Control Council
- adherence to standards
- reporting of adverse reactions and technical errors
- advertising of medicines
- Narcotic and Psychotropic substances control

16.3.3 Narcotics/Psychotropics

South Africa is co-signatory to the 1961 Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances of the International Narcotics Control Board (INCB). The said Conventions as well as the Medicines and Related Substances Act, 1965 (Act 101 of 1965) require that annual returns on all sales of narcotic and psychotropic substances be submitted to the INCB in Vienna, Austria, before 28 February each year.

Manufacturers and wholesalers must keep registers of quantities of specified Schedule 5 and Schedule 6 substances that were

- held in stock on the 1st of January and the 31st of December each year;
- destroyed, lost or stolen;
- acquired by importation of the substance as a raw material or as contained in a preparation, local production of the raw material and local purchasing of the raw material;
- used in the production of any other specified Schedule 5, Schedule 6, Schedule 7 or any other scheduled substances;
- used in the manufacture of preparations (medicines) containing such substances; and
- sold locally or exported.

These registers must be balanced on the last day of March, June, September and December each year.

16.3.3 Narcotics/Psychotropics continued

Any person wishing to manufacture specified Schedule 5, Schedule 6, Schedule 7 or Schedule 8 substances and / or medicines containing such substances, must apply for a manufacturing permit in terms of section 22A(9)9a)9i) of Act 101 of 1965. Manufacturing permits are required for the manufacturing of all Schedule 2 preparations containing the Schedule 6 substance Cathine ((+)-norpseudoephedrine).

Importers and exporters of any specified Schedule 5 and Schedule 6 substance and / or medicines must be licensed in terms of section 22C(1)(b) of Act 101 of 1965. In addition, permits are required to import or export such substances and / or medicines. Import or export permits are required for all Schedule 2 preparations containing the Schedule 6 substance Cathine ((+)-norpseudoephedrine).

Any unusual loss or theft of narcotic or psychotropic substances and / or medicines should immediately be reported to the South African Police Services and to the office of the Registrar of Medicines.

The Medicines Control Council (MCC) prescribes the destruction of large quantities of Schedule 2 preparations [containing the Schedule 6 substance Cathine ((+)-norpseudoephedrine)], specified Schedule 5 and Schedule 6 substances and / or medicines in its "Guidelines for the Destruction of Schedule 5 / Schedule 6 medicines and substances". Destruction may only take place after a written authorisation by the MCC has been issued, specifying the quantities indicated in the request.

16.4 QUALIFICATIONS

Each person engaged in the manufacture, processing, packing or storage of a medicine shall have the education, training and experience or combination thereof, to enable that person to perform the assigned functions.

Training shall be in the particular operations that the employee performs and in general and specific GMP and written procedures as they relate to the employee's functions. Training in GMP shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to ensure that employees remain familiar with GMP requirements applicable to them.

Each person responsible for supervising the manufacture, processing, packing or storage of a medicine shall have the education, training and experience or combination thereof, to perform assigned functions in such a manner as to provide assurance that the medicine has the quality, safety, efficacy and bioavailability that it purports or is represented to possess.

There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing or storage of each medicine.

16.5 TRAINING

All Production, Quality Assurance and Stores personnel and all other personnel (e.g. maintenance, service and cleaning staff) whose duties take them into manufacturing areas, or which bear upon manufacturing activities, should be trained in the principles of GMP and in the practice (and the relevant theory) of the tasks assigned to them.

Besides the basic training on the theory and practice of GMP, 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.

Written training programs should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.

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.

To assess the effectiveness of training, checks should be carried out to confirm that designated procedures are being followed by staff at all levels.

16.5 TRAINING – cont.

Visitors or untrained personnel should not be taken into the manufacturing areas. However, if deemed necessary, they should be given information in advance, particularly about personal hygiene and prescribed protective clothing which may be required. They should be closely supervised.

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

Pharmacist Intern (Industry)

After formal university education, the Pharmacist Intern must undergo one year internship in Industry, being trained as prescribed by the Pharmacy Act.

Pharmacist's Assistant (Industry) (basic and post-basic)

After formal education by the PMA, the Pharmacist's Assistant in Industry is required to pass the Pharmacy Council's examination which enables the assistant to perform certain functions of a Pharmacist as defined by the Pharmacy Act.

16.6 HYGIENE

16.6.1 Personal Hygiene

High standards of personal cleanliness should be observed by all those concerned with production processes. (The special requirements for Sterile Products are covered in Annex 1).

Personnel should be instructed to use the hand washing facilities.

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

Eating, drinking, chewing and smoking, or the storage of food, drink, smoking materials and personal medication should not be permitted within manufacturing areas or in any other area where they might adversely influence product quality.

Direct contact should be avoided between the operators' hands and starting materials, intermediates and products (other than when they are in closed containers), as well as with any part of the equipment that comes into contact with the products.

16.6.2 Area Control

Requirements regarding personal hygiene and protective clothing apply to all persons (including visitors, maintenance personnel, senior management and inspectors) entering production areas.

All persons entering production areas should wear protective garments appropriate to the processes being carried out. The garments should be regularly and frequently cleaned and not worn outside the factory premises. Changing Rooms should be provided.

Only personnel authorised by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.

16.6.3 Medical Checks

Medical checks should be performed pre-employment and at regular intervals thereafter. Steps should be taken to ensure that no person with a disease in a communicable form, or with open lesions on the exposed surface of the body, is engaged in the manufacture of medicinal products.

Visual inspection staff should pass an annual eye examination.

Staff should be required to report infections and skin lesions and a defined procedure should be followed when they are reported. Supervisory staff should look for the signs and symptoms of these conditions.

ANNEX 17**PARAMETRIC RELEASE****17.1 PRINCIPLE**

- 17.1.1 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."
- 17.1.2 Parametric release should comply with the basic requirements of GMP, with applicable annexes and the following guidelines.

17.2 PARAMETRIC RELEASE

- 17.2.1 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.
- 17.2.2 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.

17.3 PARAMETRIC RELEASE FOR STERILE PRODUCTS

- 17.3.1 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.
- 17.3.2 A sterility test only provides an opportunity to detect a major failure of the sterility assurance system due to statistical limitations of the method.
- 17.3.3 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.
- 17.3.4 At present Parametric release can only be approved for products terminally sterilized in their final container.
- 17.3.5 Sterilization methods according to European, British or United States Pharmacopoeia requirements using steam, dry heat and ionising radiation may be considered for parametric release.
- 17.3.6 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.
- 17.3.7 A risk analysis of the sterility assurance system focused on an evaluation of releasing non-sterilised products should be performed.
- 17.3.8 The manufacturer should have a history of good compliance with GMP.
- 17.3.9 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.
- 17.3.10 A qualified experienced sterility assurance engineer and a qualified microbiologist should normally be present on the site of production and sterilization.

17.3 PARAMETRIC RELEASE FOR STERILE PRODUCTS continued

- 17.3.11 The design and original validation of the product should ensure that integrity can be maintained under all relevant conditions.
- 17.3.12 The change control system should require review of change by sterility assurance personnel.
- 17.3.13 There should be a system to control microbiological contamination in the product before sterilisation.
- 17.3.14 There should be no possibility for mix ups between sterilised and non sterilized products. Physical barriers or validated electronic systems may provide such assurance.
- 17.3.15 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.
- 17.3.16 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.
- 17.3.17 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.

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 micro-organisms 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 18

GMP GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS ¹⁰

¹⁰ South Africa has adopted the ICH GMP Guide for APIs as a Manufacturing Principle - ICH Q7A Good Manufacturing Practice for Active Pharmaceutical Ingredients
The ICH GMP Guide on APIs has been provisionally adopted by the European Commission as Annex 18 to the EC GMP Guide while the same document has been adopted as Part II of the PIC/S GMP Guide by the PIC/S Committee (PE 007) (Part II).

ANNEX 19

REFERENCE AND RETENTION SAMPLES

19.1 SCOPE

- 19.1.1 This Annex to the Guide to Good Manufacturing Practice for Medicinal Products (“the GMP Guide”) gives guidance on the taking and holding of reference samples of starting materials, packaging materials or finished products and retention samples of finished products.
- 19.1.2 Specific requirements for investigational medicinal products are given in Annex 13 to the Guide.
- 19.1.3 This annex also includes guidance on the taking of retention samples for parallel imported / distributed medicinal products.

19.2 PRINCIPLE

- 19.2.1 Samples are retained to fulfil two purposes; firstly to provide a sample for analytical testing and secondly to provide a specimen of the fully finished product. Samples may therefore fall into two categories:

Reference sample: a sample of a batch of starting material, packaging material or finished product which is stored for the purpose of being 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.

- 19.2.2 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.
- 19.2.3 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.
- 19.2.4 Records of traceability of samples should be maintained and be available for review by competent authorities.

19.3 DURATION OF STORAGE

- 19.3.1 Reference and retention samples from each batch of finished product should be retained for at least one year after the expiry date. The reference sample should be contained in its finished primary packaging or in packaging composed of the same material as the primary container in which the product is marketed (for veterinary medicinal products other than immunologicals, see also Annex 4, paragraphs 8 and 9).

19.3 DURATION OF STORAGE *continued*

- 19.3.2 Unless a longer period is required under the law of the country of manufacture (whose competent authority is a PIC/S Member), samples of starting materials (other than solvents, gases or water used in the manufacturing process) shall be retained for at least two years after the release of product. That period may be shortened if the period of stability of the material, as indicated in the relevant specification, is shorter. Packaging materials should be retained for the duration of the shelf life of the finished product concerned.

19.4 SIZE OF REFERENCE AND RETENTION SAMPLES

- 19.4.1 The reference sample should be of sufficient size to permit the carrying out, on, at least, two occasions, of the full analytical controls on the batch in accordance with the Marketing Authorisation File which has been assessed and approved by the relevant Competent Authority / Authorities. Where it is necessary to do so, unopened packs should be used when carrying out each set of analytical controls. Any proposed exception to this should be justified to, and agreed with, the relevant competent authority.
- 19.4.2 Where applicable, national requirements relating to the size of reference samples and, if necessary, retention samples, should be followed.
- 19.4.3 Reference samples should be representative of the batch of starting material, intermediate product or finished product from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g. beginning or end of a process). Where a batch is packaged in two, or more, distinct packaging operations, at least one retention sample should be taken from each individual packaging operation. Any proposed exception to this should be justified to, and agreed with, the relevant competent authority.
- 19.4.4 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.

19.5 STORAGE CONDITIONS

- 19.5.1 [...] *
- 19.5.2 Storage conditions should be in accordance with the marketing authorisation (e.g. refrigerated storage where relevant).

19.6 WRITTEN AGREEMENTS

- 19.6.1 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 PIC/S Guide to Good Manufacturing Practice. This applies also where any manufacturing or batch release activity is carried out at a site other than that with overall responsibility for the batch and the arrangements between each different site for the taking and keeping of reference and retention samples should be defined in a written agreement.
- 19.6.2 The Authorised 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.
- 19.6.3 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.

* This Section is specific to the EU GMP Guide and has not been adopted by PIC/S.

19.7 REFERENCE SAMPLES – GENERAL POINTS

- 19.7.1 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.
- 19.7.2 [...] *

19.8 RETENTION SAMPLES – GENERAL POINTS

- 19.8.1 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 Authorised Person (AP) certifying the finished product batch is located.
- 19.8.2 [...] *
- 19.8.3 Retention samples should be stored at the premises of an authorised manufacturer in order to permit ready access by the Competent Authority.
- 19.8.4 Where more than one manufacturing site is involved in the manufacture importation/packaging/testing/batch release, as appropriate of a product, the responsibility for taking and storage of retention samples should be defined in a written agreement(s) between the parties concerned.

19.9 REFERENCE AND RETENTION SAMPLES FOR PARALLEL IMPORTED / PARALLEL DISTRIBUTED PRODUCTS

Note: This section is only applicable if the national legislation deals with parallel imported / parallel distributed products.

- 19.9.1 Where the secondary packaging is not opened, only the packaging material used needs to be retained, as there is no, or little, risk of product mix up.
- 19.9.2 Where the secondary packaging is opened, for example, to replace the carton or patient information leaflet, then one retention sample, per packaging operation, containing the product should be taken, as there is a risk of product mix-up during the assembly process. It is important to be able to identify quickly who is responsible in the event of a mix-up (original manufacturer or parallel import assembler), as it would affect the extent of any resulting recall.

19.10 REFERENCE AND RETENTION SAMPLES IN THE CASE OF CLOSEDOWN OF A MANUFACTURER

- 19.10.1 Where a manufacturer closes down and the manufacturing authorisation is surrendered, revoked, or ceases to exist, it is probable that many unexpired batches of medicinal products manufactured by that manufacturer remain on the market. In order for those batches to remain on the market, the manufacturer should make detailed arrangements for transfer of reference and retention samples (and relevant GMP documentation) to an authorised storage site. The manufacturer should satisfy the Competent Authority that the arrangements for storage are satisfactory and that the samples can, if necessary, be readily accessed and analysed.
- 19.10.2 If the manufacturer is not in a position to make the necessary arrangements this may be delegated to another manufacturer. The Marketing Authorisation holder (MAH) is responsible for such delegation and for the provision of all necessary information to the Competent Authority.

* This Section is specific to the EU GMP Guide and has not been adopted by PIC/S.

ANNEX 20

QUALITY RISK MANAGEMENT

FOREWORD AND SCOPE OF APPLICATION

The new GMP Annex 20 corresponds to ICH Q9 guideline on Quality Risk Management. It provides guidance on a systematic approach to quality risk management facilitating compliance with GMP and other quality requirements. It includes principles to be used and options for processes, methods and tools, which may be used when applying a formal quality risk management approach.

To ensure coherence, GMP Part I, Chapter 1 on Quality Management, has been revised to include aspects of quality risk management within the quality system framework. A similar revision is planned for Part II of the Guide. Other sections of the GMP Guide may be adjusted to include aspects of quality risk management in future broader revisions of those sections.

With the revision of the chapters on quality management in GMP Parts I and II quality risk management becomes an integral part of a manufacturer's quality system. Annex 20 itself is not intended, however, to create any new regulatory expectations; it provides an inventory of internationally acknowledged risk management methods and tools together with a list of potential applications at the discretion of manufacturers.

It is understood that the ICH Q9 guideline was primarily developed for quality risk management of medicinal products for human use. With the implementation in Annex 20 benefits of the guideline, such as processes, methods and tools for quality risk management are also made available to the veterinary sector.

While the GMP guide is primarily addressed to manufacturers, the ICH Q9 guideline, has relevance for other quality guidelines and includes specific sections for regulatory agencies.

However, for reasons of coherence and completeness, the ICH Q9 guideline has been transferred completely into GMP Annex 20.

20.1 INTRODUCTION

Risk management principles are effectively utilized in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. Although there are some examples of the use of *quality risk management* in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. In addition, the importance of *quality systems* has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system.

It is commonly understood that *risk* is defined as the combination of the probability of occurrence of *harm* and the *severity* of that harm. However, achieving a shared understanding of the application of risk management among diverse *stakeholders* is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm.

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

The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk.

20.1 INTRODUCTION – cont.

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
- provide regulators with greater assurance of a company's ability to deal with potential risks
- beneficially affect the extent and level of direct regulatory oversight.

The purpose of this document is to offer a systematic approach to quality risk management.

It serves as a foundation or resource document that is independent of, yet supports other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment.

It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk based decisions, both by regulators and industry, regarding the quality of drug substances and drug (medicinal) products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements.

It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/ or internal procedures e.g. standard operating procedures). The use of informal risk management processes (using empirical tools and/ or internal procedures) can also be considered acceptable.

Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators.

20.2 SCOPE

This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality.

These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labelling materials in drug (medicinal) products, biological and biotechnological products).

20.3 PRINCIPLES OF QUALITY RISK MANAGEMENT

Two primary principles of quality risk management are:

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

20.4 GENERAL QUALITY RISK MANAGEMENT PROCESS

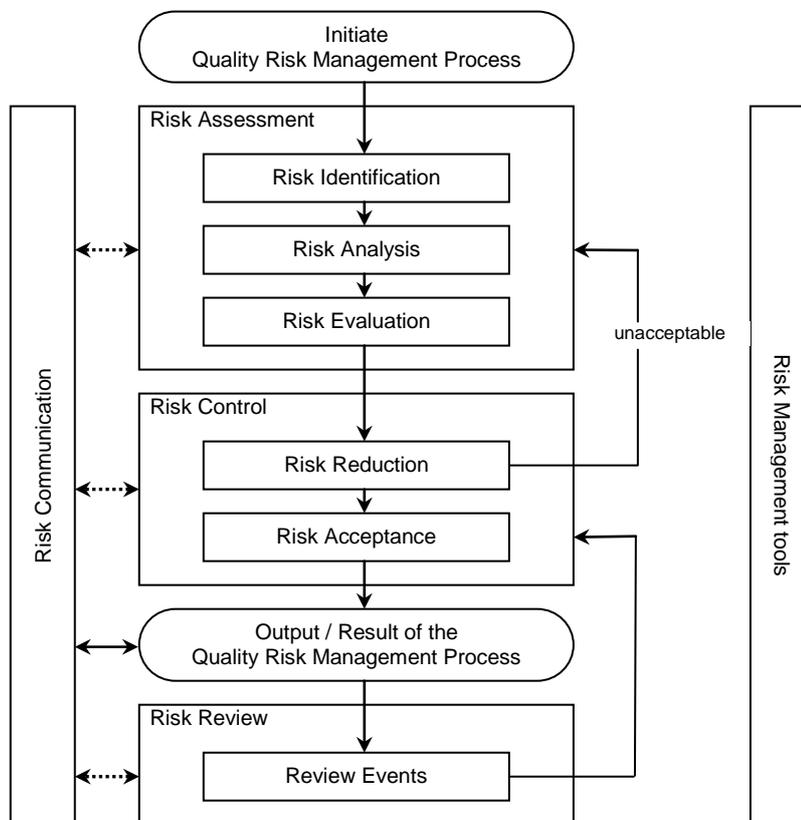
Quality risk management is a systematic process for the

- assessment,
- control,
- communication and
- review of risks to the quality of the drug (medicinal) product across the product lifecycle.

A model for quality risk management is outlined in the diagram (Figure 1).

Other models could be used. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Figure 1: Overview of a typical quality risk management process



Decision nodes are not shown in the diagram above because decisions can occur at any point in the process.

These decisions might be

- to return to the previous step and seek further information,
- to adjust the risk models or
- even to terminate the risk management process based upon information that supports such a decision.

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

20.4.1 Responsibilities

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

Decision *makers* should:

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

20.4.2 Initiating a Quality Risk Management Process

Quality risk management should include systematic processes designed to coordinate, facilitate and improve science-based decision making with respect to risk.

Possible steps used to initiate and plan a quality risk management process might include the following:

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

20.4.3 Risk Assessment

Risk assessment consists of

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

Quality risk assessments begin with a well-defined problem description or risk question.

When the risk in question is well defined, an appropriate risk management tool (see examples in section 5) and the types of information needed to address the risk question will be more readily identifiable.

As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

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

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description.

Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders.

Risk identification addresses the “What might go wrong?” question, including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

Risk analysis is the estimation of the risk associated with the identified hazards.

It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms.

In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria.

Risk evaluations consider the strength of evidence for all three of the fundamental questions.

In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output.

Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help identify its limitations.

Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability.

Typical sources of uncertainty include gaps in knowledge gaps in pharmaceutical science and process understanding, sources of harm (e.g. failure modes of a process, sources of variability), and probability of detection of problems.

The output of a risk assessment is either a *quantitative* estimate of risk or a *qualitative description* of a range of risk.

- When risk is expressed *quantitatively*, a numerical probability is used.
- Alternatively, risk can be expressed using *qualitative* descriptors, such as “high”, “medium”, or “low”, which should be defined in as much detail as possible.

Sometimes a "risk score" is used to further define descriptors in risk ranking.

In quantitative risk assessments, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a time.

Alternatively, some risk management tools use a relative risk measure to combine multiple levels of severity and probability into an overall estimate of relative risk. The intermediate steps within a scoring process can sometimes employ quantitative risk estimation.

20.4.4 Risk Control

Risk control includes decision making to reduce and/or accept risks.

The purpose of risk control is to **reduce** the risk to an acceptable level.

The amount of effort used for risk control should be proportional to the significance of the risk.

Decision makers might use different processes, including benefit-cost analysis, for understanding the optimal level of risk control.

Risk control might focus on the following questions:

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

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level (see Fig. 1).

Risk reduction might include actions taken to mitigate the severity and probability of harm.

Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy.

The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk.

Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified.

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

20.4.5 Risk Communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others.

Parties can communicate at any stage of the risk management process (see Fig. 1: dashed arrows).

The output/result of the quality risk management process should be appropriately communicated and documented (see Fig. 1: solid arrows).

Communications might include those among interested parties; e.g. regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc.

The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability or other aspects of risks to quality.

Communication need not be carried out for each and every risk acceptance. Between the industry and regulatory authorities, communication concerning quality risk management decisions might be effected through existing channels as specified in regulations and guidances.

20.4.6 Risk Review

Risk management should be an ongoing part of the quality management process.

A mechanism to review or monitor events should be implemented.

The output/results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g. results of product review, inspections, audits, change control) or unplanned (e.g. root cause from failure investigations, recall).

The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions (section 4.4).

20.5 RISK MANAGEMENT METHODOLOGY

Quality risk management supports a scientific and practical approach to decision-making.

It provides documented, transparent and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity and sometimes detectability of the risk.

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

Additionally, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/ or internal procedures (e.g. standard operating procedures).

Below is a non-exhaustive list of some of these tools (further details in Annex 1 and chapter 8):

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

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

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

20.6 INTEGRATION OF QUALITY RISK MANAGEMENT INTO INDUSTRY AND REGULATORY OPERATIONS

Quality risk management is a process that supports science-based and practical decisions when integrated into quality systems (see Addendum II). As outlined in the introduction, appropriate use of quality risk management does not obviate industry's obligation to comply with regulatory requirements. However, effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight. In addition, quality risk management can facilitate better use of resources by all parties.

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

Quality risk management should be integrated into existing operations and documented appropriately. Addendum 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.

20.6 INTEGRATION OF QUALITY RISK MANAGEMENT INTO INDUSTRY AND REGULATORY OPERATIONS – cont.

Examples for industry and regulatory operations (see Addendum II):

- Quality management

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

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

Examples for regulatory operations (see Addendum II):

- Inspection and assessment activities

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

20.7 DEFINITIONS

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

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

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

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

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

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

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

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

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

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

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

Risk analysis – the estimation of the risk associated with the identified hazards

Risk assessment – a systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

20.7 **DEFINITIONS – cont.**

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)

20.8 **REFERENCES**

ICH Q8 Pharmaceutical development

ISO/IEC Guide 73:2002 - Risk Management - Vocabulary - Guidelines for use in Standards

ISO/IEC Guide 51:1999 - Safety Aspects - Guideline for their inclusion in standards

Process Mapping by the American Productivity & Quality Center 2002, ISBN 1928593739

IEC 61025 - Fault Tree Analysis (FTA)

IEC 60812 Analysis Techniques for system reliability—Procedures for failure mode and effects analysis (FMEA)

Failure Mode and Effect Analysis, FMEA from Theory to Execution, 2nd Edition 2003, D. H. Stamatis, ISBN 0873895983

Guidelines for Failure Modes and Effects Analysis (FMEA) for Medical Devices, 2003 Dyadem Press ISBN 0849319102

The Basics of FMEA, Robin McDermott, Raymond J. Mikulak, Michael R. Beauregard 1996 ISBN 0527763209

WHO Technical Report Series No 908, 2003 Annex 7 Application of Hazard Analysis and Critical Control Point (HACCP) methodology to pharmaceuticals

IEC 61882 - Hazard Operability Analysis (HAZOP)

ISO 14971:2000 - Application of Risk Management to Medical Devices

ISO 870:1993 - Control Charts

ISO 7871:1997 - Cumulative Sum Charts

ISO 7966:1993 - Acceptance Control Charts

ISO 8258:1991 - Shewhart Control Charts

What is Total Quality Control?; The Japanese Way, Kaoru Ishikawa (Translated by David J. Liu), 1985, ISBN 0139524339

ADDENDUM I: RISK MANAGEMENT METHODS AND TOOLS

The purpose of this addendum 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.

20-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)

20-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.

20-I.3 Failure Mode, Effects and Criticality Analysis (FMECA)

FMECA 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.

20-I.3 Failure Mode, Effects and Criticality Analysis (FMECA) – cont.

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.

20-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.

20-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.

20-I.5 Hazard Analysis and Critical Control Points (HACCP) – cont.

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.

20-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.

20-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,
- (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.

20-I.7 Preliminary Hazard Analysis (PHA) - Potential Areas of Use(s)- cont.

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.

20-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.

20-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

ADDENDUM II: POTENTIAL APPLICATIONS FOR QUALITY RISK MANAGEMENT

This addendum 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 addendum is not intended to create any new expectations beyond the current regulatory requirements.

20-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

20-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)).

20-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)

20-II.3 Quality Risk Management as Part of development – cont.

- 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)

20-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

20-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)

20-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

20-II.6 *Quality Risk Management as Part of Production Validation – cont.*

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)

20-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

20-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.

Authorised person

Person recognised by the international authority as having the necessary basic scientific and technical background and experience, or in the case of the South African MCC, the responsible pharmacist.

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 sub-batches, 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

Micro-organisms, including genetically engineered micro-organisms, cell cultures and endoparasites, whether pathogenic or not.

Bulk product

Any product which has completed all processing stages up to, but not including, final packaging.

Calibration

The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by a material measure, and the corresponding known values of a reference standard.

GLOSSARY continued

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 Annex 1 on the Manufacture of sterile medicinal products.

Clean/contained area

An area constructed and operated in such a manner that will achieve the aims of both a clean area and a contained area at the same time.

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.

GLOSSARY *continued***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 products 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.

Legally authorised person

A pharmacist, pharmacist student, pharmacist intern, post basic assistant, etc registered with the Pharmacy Council, as appropriate for the action within the scope of a pharmacist.

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.

GLOSSARY *continued***Manufacturer**

Holder of a manufacturing licence, and is specified in the relevant medicine registration dossier.

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 product

Any medicine or similar product intended for human use, which is subject to control under health legislation in South Africa.

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" shall mean any medicinal product which, when ready for use, contains 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.

GLOSSARY *continued***Recovery**

The introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture.

Reprocessing

The reworking of all or part of a batch of product of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.

Return

Sending back to the manufacturer or distributor of a medicinal product which may or may not present a quality defect.

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 a medicinal product, but excluding packaging materials.

Sterility

Sterility is the absence of living organisms. The conditions of the sterility tests are given in the European, British or United States Pharmacopoeia.¹¹

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).

¹¹ 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.