TGA THERAPEUTIC GOODS ADMINISTRATION

Commonwealth Department of Health and Ageing

## Therapeutic Goods Administration

# AUSTRALIAN CODE OF GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS

**16 August 2002**

This Code is based entirely on the "Guide to Good Manufacturing Practice for Medicinal Products", version PH 1/97 (Rev. 3), dated 15 January 2002, published by the Pharmaceutical Inspection Cooperation Scheme (PIC/S). The modifications to that Guide, and its adoption as the Australian Code of Good Manufacturing Practice, is done so with the expressed permission of the PIC/S.

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**ANNEXES**

Ψ This PIC/S Annex is not adopted by the Australian Code of Good Manufacturing Practice for Medicinal Products, 16 August 2002.

* This Annex is specific to the EU GMP Guide and has not been adopted by Australia.

** Australia has adopted the ICH GMP Guide for APIs as a Manufacturing Principle.

# CODE OF GOOD MANUFACTURING PRACTICE

# FOR MEDICINAL PRODUCTS

## INTRODUCTION

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 throughout Europe, it was agreed to harmonise the rules of GMP applied under Pharmaceutical Inspection Convention (PIC) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) with those of the EU Guide to Good Manufacturing Practice for Medicinal Products and its Annexes.

A minimum of editorial changes have, however, been necessary to adapt the text of the EU Guide to the Convention's purposes and requirements. Those changes are the following:

- the definition of Pharmaceutical Product (referred to as “Medicinal Product” in this Code) which is found in Article 1 of the Pharmaceutical Inspection Convention has been retained;
- references to the EU Directives have been deleted;
- as the expression "Qualified Person" does not exist under the PIC or PIC/S , it has been replaced by "authorised person" (see Glossary)"
- 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 Code has been amended to read "European or other relevant Pharmacopoeia".

The standards and principles contained in this Code are intended to serve as a reference for the preparation of information on manufacturing practice as requested under the Pharmaceutical Inspection Convention or the Pharmaceutical Inspection Co-operation Scheme.

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.

In addition to the general matters of Good Manufacturing Practice outlined in the chapters of this Code, supplementary Annexes have been incorporated. The purpose

of the supplementary Annexes on other subjects is to provide details about specific areas of activity which may not necessarily apply to all manufacturers.

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.

It is recognised that there are acceptable methods, other than those describe in this Code, which are capable of achieving the principles of the Code. This Code 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 Code.

## INTERPRETATION

For the purposes of this Code, the words “should” and “shall” appearing in each of the Chapters 1 to 9 inclusive in the Code, and in each of the Annexes 1 to 17 inclusive in the Code, mean “must” and the activities, descriptions or specifications accompanied by the word “should” or “shall” are to be read as mandatory, unless the manufacturer is able to demonstrate that the activity, description or specification is inapplicable or can be replaced by an alternative which must be demonstrated to provide at least an equivalent level of quality assurance.

# CHAPTER 1

## QUALITY MANAGEMENT

## PRINCIPLE

The holder of a manufacturing authorization must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers and by the distributors. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality Assurance Incorporating Good Manufacturing Practice and thus Quality Control. It should be fully documented and its effectiveness monitored. All parts of the Quality Assurance systems should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment and facilities. There are additional legal responsibilities for the holder of the manufacturing authorization and for the authorised person(s).

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

## QUALITY ASSURANCE

1.2. 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 object 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 Code.

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 and Good Laboratory 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 marketing authorization and any other regulations relevant to the production, control and release of medicinal products;

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

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

## GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS (GMP)

1.3. 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 marketing authorization or product specification.

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

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

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

iii. all necessary facilities for GMP are provided including:

a. appropriately qualified and trained personnel;

b. adequate premises and space;

c. suitable equipment and services;

d. correct materials, containers and labels;

e. approved procedures and instructions;

f. suitable storage and transport;

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

v. operators are trained to carry out procedures correctly;

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

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

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

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

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

## QUALITY CONTROL

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

The basic requirements of Quality Control are that:

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

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

iii. test methods are validated;

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

v. the finished products contain active ingredients complying with the qualitative and quantitative composition of the marketing authorization, are of the purity required, and are enclosed within their proper container 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 marketing authorization;

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.

# CHAPTER 2

## PERSONNEL

## PRINCIPLE

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

## GENERAL

2.1. The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

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

## KEY PERSONNEL

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

2.4. ...

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

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

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

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

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

v. to ensure that the appropriate validations are done;

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

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

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

ii. to evaluate batch records;

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

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

v. to approve and monitor any contract analysts;

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

vii. to ensure that the appropriate validations are done;

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

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

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

- the authorization of written procedures and other documents, including amendments;
- the monitoring and control of the manufacturing environment;
- plant hygiene;
- process validation;
- training;
- the approval and monitoring of suppliers of materials;
- the approval and monitoring of contract manufacturers;
- the designation and monitoring of storage conditions for materials and products;

- the retention of records;
- the monitoring of compliance with the requirements of GMP;
- the inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality.

## TRAINING

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

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

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

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

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

## PERSONAL HYGIENE

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

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

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

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

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

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

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

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

# CHAPTER 3

# PREMISES AND EQUIPMENT

## PRINCIPLE

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

## PREMISES

### General

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

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

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

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

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

### Production Area

3.6. In order to minimise the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular medicinal products, such as highly sensitising materials (e.g. penicillins) or biological preparations (e.g. from live micro-organisms). The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and non-medicinal products should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working in the same facilities can

be accepted provided that specific precautions are taken and the necessary validations are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.

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

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

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

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

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

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

3.13. Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.

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

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

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

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

### Storage Areas

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

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

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

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

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

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

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

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

### Quality Control Areas

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

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

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

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

### Ancillary Areas

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

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

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

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

## EQUIPMENT

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

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

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

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

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

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

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

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

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

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

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

# CHAPTER 4

# DOCUMENTATION

## PRINCIPLE

Good documentation constitutes an essential part of the quality assurance system. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history. Specifications, Manufacturing Formulae and instructions, procedures, and records must be free from errors and available in writing. The legibility of documents is of paramount importance.

## GENERAL

4.1. *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.

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

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

*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. Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorization dossiers.

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

4.4. 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.

4.5. 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.

4.6. 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.

4.7. 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.

4.8. 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. They should be retained for at least one year after the expiry date of the finished product.

4.9. 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. 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,.

## DOCUMENTS REQUIRED

### Specifications

4.10 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.

### Specifications for starting and packaging materials

4.11. 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.

### Specifications for intermediate and bulk products

4.12. 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.

### Specifications for finished products

4.13. Specifications for finished products should include:

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

b) the formula 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.

## MANUFACTURING FORMULA AND PROCESSING INSTRUCTIONS

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

4.14. The Manufacturing Formula should include:

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

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

c) a list of all starting materials to be used, with the amount of each, described 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.

4.15. 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, pretreatments, 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.

## PACKAGING INSTRUCTIONS

4.16. 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.

## BATCH PROCESSING RECORDS

4.17. A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions. 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.

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 Formula and Processing Instructions.

## BATCH PACKAGING RECORDS

4.18. 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.

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.

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 Formula 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.

## PROCEDURES AND RECORDS

### Receipt

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

4.20. 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).

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

### Sampling

4.22. 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 13).

### Testing

4.23. 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 17).

### Other

4.24 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.

4.25. 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).

4.26. 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.

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

4.28. 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.

4.29. 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

## PRINCIPLE

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

## GENERAL

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

## PREVENTION OF CROSS-CONTAMINATION IN PRODUCTION

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

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

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

b) providing appropriate air-locks and air extraction;

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

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

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

f) using "closed systems" of production;

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

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

## VALIDATION

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

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

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

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

## STARTING MATERIALS

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

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

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

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

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

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

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

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

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

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

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

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

## PROCESSING OPERATIONS INTERMEDIATE AND BULK PRODUCTS

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

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

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

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

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

## PACKAGING MATERIALS

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

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

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

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

## PACKAGING OPERATIONS

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

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

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

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

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

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

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

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

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

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

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

a) general appearance of the packages;

b) whether the packages are complete;

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

d) whether any over-printing is correct;

e) correct functioning of line monitors.

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

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

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

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

## FINISHED PRODUCTS

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

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

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

## REJECTED, RECOVERED AND RETURNED MATERIALS

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

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

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

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

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

# CHAPTER 6

# QUALITY CONTROL

## PRINCIPLE

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

## GENERAL

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

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

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

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

## GOOD QUALITY CONTROL LABORATORY PRACTICE

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

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

## DOCUMENTATION

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

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

6.8. Any Quality Control documentation relating to a batch record should be retained for one year after the expiry date of the batch.

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

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

## SAMPLING

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

- the method of sampling;
- the equipment to be used;
- the amount of the sample to be taken;

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

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

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

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

## TESTING

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

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

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

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

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

c) references to the relevant specifications and testing procedures;

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

e) dates of testing;

f) initials of the persons who performed the testing;

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

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

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

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

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

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

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

# CHAPTER 7

# CONTRACT MANUFACTURE AND ANALYSIS

## PRINCIPLE

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

## GENERAL

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

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

## THE CONTRACT GIVER

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

7.4. The Contract Giver should provide the Contract Acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials or other products.

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

## THE CONTRACT ACCEPTOR

7.6. The Contract Acceptor must have adequate premises and equipment, knowledge and experience, and competent personnel to carry out satisfactorily

the work ordered by the Contract Giver. Contract manufacture may be undertaken only by a manufacturer who is the holder of a manufacturing authorization.

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

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

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

## THE CONTRACT

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

7.11. 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 Marketing Authorization.

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

7.13. Manufacturing, analytical and distribution records, and reference samples should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the Contract Giver.

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

7.15. In case of contract analysis, the Contract Acceptor should understand that he is subject to inspection by the competent Authorities, which in Australia is the Therapeutic Goods Administration of the Commonwealth Department of Health and Ageing.

# CHAPTER 8

# COMPLAINTS AND PRODUCT RECALL

## PRINCIPLE

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

## COMPLAINTS

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

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

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

8.4. If a product defect is discovered or suspected in a batch, 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.

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

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

8.7. The Competent Authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, or any other serious quality problems with a product.

## RECALLS

8.8. 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.

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

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

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

8.12. 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.

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

8.14. 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.

8.15. The effectiveness of the arrangements for recalls should be evaluated from time to time.

# CHAPTER 9

## SELF INSPECTION

## PRINCIPLE

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

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

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

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

# ANNEX 1

# MANUFACTURE OF STERILE MEDICINAL PRODUCTS

## PRINCIPLE

The manufacture of sterile products is subject to special requirements in order to minimise risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance bears a particularly great importance 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 is made to other compendia such as the CEN/ISO Standards.

## GENERAL

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

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

3. Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimise the risks of particulate or microbial contamination of the product or materials being handled.

   In order to meet “in operation” conditions these areas should be designed to reach certain specified air-cleanliness levels in the “at-rest” occupancy state. The “at-rest” state is the condition where the installation is complete with production equipment installed and operating 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.

For the manufacture of sterile medicinal products normally 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 an homogeneous air speed of 0.45 m/s +/- 20% (guidance value) at the working position.

Grade B: In case of aseptic preparation and filling 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 | |
|---|---|---|---|---|
| Grade | Maximum permitted number of particles/m3 equal to or above | | | |
| | 0,5μm | 5μm | 0,5μm | 5μ |
| A | 3 500 | 0 | 3 500 | 0 |
| B[a] | 3 500 | 0 | 350 000 | 2 000 |
| C[a] | 350 000 | 2 000 | 3 500 000 | 20 000 |
| D[a] | 3 500 000 | 20 000 | not defined [c] | not defined [c] |

Notes: [a] 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 filters such as HEPA for grades A, B and C.

[b] The guidance given for the maximum permitted number of particles in the "at rest" condition corresponds approximately to the US Federal Standard 209 E and the ISO classifications as follows: grades A and B correspond with class 100, M 3.5, ISO 5; grade C with class 10 000, M 5.5, ISO 7 and grade D with class 100 000, M 6.5, ISO 8.

[c] The requirement and limit for this area will depend on the nature of the operations carried out.

Examples of operations to be carried out in the various grades are given in the table below (see also para. 11 and 12)

| Grade | Examples of operations for terminally sterilised products (see para. 11) |
|---|---|
| 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 para. 12) |
|---|---|
| A | Aseptic preparation and filling |
| C | Preparation of solutions to be filtered |
| D | Handling of components after washing |

The particulate conditions given in the table for the "at-rest" state should be achieved in the unmanned state after a short "clean up" period of 15-20 minutes (guidance value), 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.

4. In order to control the particulate cleanliness of the various grades in operation, the areas should be monitored.

5. In order to control the microbiological cleanliness of the various grades in operation, the areas should be monitored.

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 sanitation.

Recommended limits for microbiological monitoring of clean areas in operation:

| | Recommended limits for microbial contamination[a] | | | |
|---|---|---|---|---|
| Grade | Air sample cfu/m3 | 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

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.

## ISOLATOR TECHNOLOGY

7. 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.

8. 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.

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

## BLOW/FILL/SEAL TECHNOLOGY

10. 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.

    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, and interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

## TERMINALLY STERILISED PRODUCTS

11. 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.

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

    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.

## ASEPTIC PREPARATION

12. 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.

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.

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

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.

Preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment, with a grade B background, when the product is exposed and is not subsequently filtered.

## PERSONNEL

13. 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.

14. 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.

15. 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.

16. 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.

17. Changing and washing should follow a written procedure designed to minimise contamination of clean area clothing or carry-through of contaminants to the clean areas.

18. Wristwatches, make-up and jewellery should not be worn in clean areas.

19. 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.

The description of clothing required for each grade is given below:

Grade D: Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.

Grade C: Hair and, where relevant, beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibres or particulate matter.

Grade A/B: Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilised, non-powdered rubber or plastic gloves and sterilised or disinfected footwear should be worn. Trouser-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.

20. 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, or at least once a day if monitoring results justify this. Gloves should be regularly disinfected during operations. Masks and gloves should be changed at least at every working session.

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

## PREMISES

22. 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.

23. 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.

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

25. 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.

26. 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.

27. 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.

28. 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.

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

30. 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.

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

## EQUIPMENT

32. 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).

33. 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.

34. 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.

35. 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.

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

## SANITATION

37. 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.

38. 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.

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

## PROCESSING

40. Precautions to minimise contamination should be taken during all processing stages including the stages before sterilisation.

41. 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.

42. 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.

43. Care should be taken that any validation does not compromise the processes.

44. 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.

45. 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.

46. 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.

47. Containers and materials liable to generate fibres should be minimised in clean areas.

48. Where appropriate, measures should be taken to minimise the particulate contamination of the end product.

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

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

51. 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.

52. 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.

53. 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.

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

## STERILISATION

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

56. 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.

57. 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.

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

59. Biological indicators should be considered as an additional method for monitoring the sterilisation. They should be stored and used according to the manufacturers 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.

60. 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.

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

## STERILISATION BY HEAT

62. 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.

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

64. 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.

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

## MOIST HEAT

66. 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.

67. 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.

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

## DRY HEAT

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

## STERILISATION BY RADIATION

70. 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.

71. 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.

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

73. Validation procedures should ensure that the effects of variations in density of the packages are considered.

74. 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.

75. The total radiation dose should be administered within a predetermined time span.

## STERILISATION WITH ETHYLENE OXIDE

76. 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.

77. 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.

78. 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.

79. 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.

80. 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.

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

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

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

83. 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.

84. Fibre shedding characteristics of filters should be minimal.

85. 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.

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

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

## FINISHING OF STERILE PRODUCTS

88. 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.

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

90. Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eye-sight checks, with spectacles if worn, and be allowed frequent breaks from

inspection. Where other methods of inspection are used, the process should be validated and the performance of the equipment checked at intervals. Results should be recorded.

## QUALITY CONTROL

91. 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.

92. 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.

93. 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

## 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[1]:

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 Annex may necessarily apply to products in category a.)

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

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

## PRINCIPLE

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.

Unlike conventional medicinal products, which are reproduced using chemical and physical techniques capable of a high degree of consistency, the

[1] 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).

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.

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.

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.

## PERSONNEL

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. 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.

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.

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.

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.

## PREMISES AND EQUIPMENT

6. 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.

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

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

9. Dedicated facilities should be used for the handling of Bacillus anthracis, of Clostridium botulinum and of Clostridium tetani until the inactivation process is accomplished.

10. Production on a campaign basis may be acceptable for other spore forming organisms provided that the facilities are dedicated to this group of products and not more than one product is processed at any one time.

11. Simultaneous production in the same area using closed systems of biofermenters may be acceptable for products such as monoclonal antibodies and products prepared by r-DNA techniques.

12. Processing steps after harvesting may be carried out simultaneously in the same production area provided that adequate precautions are taken to prevent cross-contamination. For killed vaccines and toxoids, such parallel processing should only be performed after inactivation of the culture or after detoxification.

13. 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.

14. Air handling units should be specific to the processing area concerned and recirculation of air should not occur from areas handling live pathogenic organisms.

15. 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.

16. Equipment used during handling of live organisms should be designed to maintain cultures in a pure state and uncontaminated by external sources during processing.

17. 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.

18. Primary containment should be designed and tested to demonstrate freedom from leakage risk.

19. Effluents which may contain pathogenic microorganisms should be effectively decontaminated.

20. 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.

## ANIMAL QUARTERS AND CARE

21. Animals are used for the manufacture of a number of biological products, for example polio vaccine (monkeys), snake antivenoms (horses and goats), rabies vaccine (rabbits, mice and hamsters) and serum gonadotropin (horses). 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).

22. 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.

## DOCUMENTATION

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

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

# PRODUCTION

## Starting materials

25. The source, origin and suitability of starting materials 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.

26. 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).

## Seed lot and cell bank system

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

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

29. 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.

30. 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.

31. 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.

32. 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.

33. 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.

### Operating principles

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

35. 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.

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

37. If possible, media 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.

38. Careful consideration should be given to the validation of any necessary virus removal or inactivation undertaken.

39. 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.

40. 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.

## QUALITY CONTROL

41. 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.

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

43. Continuous monitoring of certain production processes is necessary, for example fermentation. Such data should form part of the batch record.

44. 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

## PRINCIPLE

The manufacturing and handling of radiopharmaceuticals is potentially hazardous. The types of radiation emitted and the half-lives of the radioactive isotopes are parameters contributing to the level of risk. Particular attention must be paid to the prevention of cross-contamination, to the retention of radionuclide contaminants, and to waste disposal. Special consideration may be necessary with reference to the small batch sizes made frequently for many radiopharmaceuticals. 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.

Note: The manufacture of radiopharmaceuticals must be undertaken in accordance with the Good Manufacturing Practice described in this Code and also in the supplementary Annexes such as those for sterile preparations where appropriate. Some points are nevertheless specific to the handling of radioactive products and are modified by or detailed in these supplementary Annexes. This manufacture must comply with the requirements of EURATOM Directives laying down the basic standards for the health protection of the general public and workers against the dangers of ionising radiation, as well as with other relevant national requirements.

## PERSONNEL

1. 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. In particular, the personnel should be given detailed information and appropriate training on radiation protection.

## PREMISES AND EQUIPMENT

2. Radioactive products should be stored, processed, packaged and controlled in dedicated and self-contained facilities. Equipment used for manufacturing operations should be reserved for radiopharmaceuticals.

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.

4. For sterile products the working zone where products or containers may be exposed should comply with the environmental requirements described in the Supplement on Sterile Products. This may be achieved by the provision within the work station of a laminar flow of HEPA-filtered air and by fitting air-locks to entry ports. Total containment work stations may provide these requirements. They should be in an environment conforming to at least grade D.

5. Air extracted from areas where radioactive products are handled should not be recirculated; air outlets should be designed to avoid possible environmental contamination of radioactive particles and gases.

   There should be a system to prevent air entering the clean area through extract ducts e.g. when the extract fan is not operating.

## PRODUCTION

6. Production of different radioactive products in the same work stations and at the same time should be avoided in order to minimise the risk of cross-contamination or mix-up.

7. Process validation, in-process controls and monitoring of process parameters and environment assume particular importance in cases where it is necessary to take the decision to release or reject a batch or a product before all tests are completed.

## QUALITY CONTROL

8. When products must be dispatched before all tests are completed, this does not reduce the need for a formal recorded decision to be taken by the Authorised Person on the conformity of the batch. In this case there should be a written procedure detailing all production and Quality Control data which should be considered before the batch is dispatched. A procedure should also describe those measures which will be taken by the Authorised Person if unsatisfactory test results are obtained after dispatch.

9. Unless otherwise specified in the marketing authorization, reference samples of every batch should be retained.

## DISTRIBUTION AND RECALLS

10. Detailed distribution records should be maintained and there should be procedures which describe the measures to be taken for stopping the use of defective radiopharmaceuticals. Recall operations should be shown to be operable within a very short time.

# [ANNEX 4]

## [MANUFACTURE OF VETERINARY MEDICINAL PRODUCTS OTHER THAN IMMUNOLOGICALS]Ψ



Ψ This PIC/S Annex is not adopted by the Australian Code of Good Manufacturing Practice for Medicinal Products, 16 August 2002.

# [ANNEX 5]

## [MANUFACTURE OF IMMUNOLOGICAL VETERINARY MEDICAL PRODUCTS ]Ψ



Ψ This PIC/S Annex is not adopted by the Australian Code of Good Manufacturing Practice for Medicinal Products, 16 August 2002.

# ANNEX 6

# MANUFACTURE OF MEDICINAL GASES

## 1. PRINCIPLE

This Annex deals with industrial manufacturing of medicinal gases, which is a specialised industrial process not normally undertaken by pharmaceutical companies.

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.

## 2. PERSONNEL

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

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.

## 3. PREMISES AND EQUIPMENT

### 3.1 Premises

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.

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.

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.

### 3.2 Equipment

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

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.)

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

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.

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.

## 4. DOCUMENTATION

4.1 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 point 5.3.5);
- 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.

# 5. PRODUCTION

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

### 5.2 Bulk production

5.2.1 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 national competent authority.

5.2.2 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.

5.2.3 All separation and purification steps should be designed to operate at optimal effectiveness. For example, impurities that may adversely affect a purification step should be removed before this step is reached.

5.2.4 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.

5.2.5 If applicable, limits for process temperatures should be documented and in-process monitoring should include temperature measurement.

5.2.6 Computer systems used in controlling or monitoring processes should be validated.

5.2.7 For continuous processes, a definition of a batch should be documented and related to the analysis of the bulk gas.

5.2.8 Gas production should be continuously monitored for quality and impurities.

5.2.9 Water used for cooling during compression of air should be monitored for microbiological quality when in contact with the medicinal gas.

5.2.10 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. 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.

5.2.11 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.

5.2.12 Bulk gases intended for medicinal use should be defined as a batch, controlled in accordance with relevant Pharmacopoeial monographs and released for filling.

**5.3 Filling and labelling**

5.3.1 For filling of medicinal gases the batch should be defined.

5.3.2 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.

5.3.3 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 3.2.2). There should be a system in place ensuring traceability of cylinders and valves.

5.3.4 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.

5.3.5 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.

5.3.6 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.

5.3.7 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.

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

5.3.9 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. QUALITY CONTROL

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

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.

6.3 The bulk gas supply should be released for filling. (see 5.2.12)

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.

6.5 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 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.

6.7 When gases are mixed in-line before filling (e.g. nitrous oxide/oxygen mixture) continuous analysis of the mixture being filled is required.

6.8 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.

6.9 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.

6.10 In the case of cryogenic gas filled into cryogenic home vessels for delivery to users, each vessel should be tested for identity and assay.

6.11 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.

6.12 Retained samples are not required, unless otherwise specified.

## 7. STORAGE AND RELEASE

7.1 Filled cylinders should be held in quarantine until released by the authorised person.

7.2 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.

7.3 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.

7.4 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 Code of 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 -50$^0$ 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 –150$^0$ 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 +15$^0$ C or has a vapour pressure exceeding 3 bar (300 kPa) at +50$^0$ 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 –50$^0$ C.

***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 retropollution 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

## PRINCIPLE

Because of their often complex and variable nature, and the number and small quantity of defined active ingredients, control of starting materials, storage and processing assume particular importance in the manufacture of herbal medicinal products.

## PREMISES

### Storage areas

1. Crude (i.e. unprocessed) plants should be stored in separate areas. The storage area should be well ventilated and 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 microorganisms brought in with the crude plant and to prevent cross-contamination. Containers should be located in such a way as to allow free air circulation.

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

3. Storage of plants, extracts, tinctures and other preparations may require special conditions of humidity, temperature or light protection; these conditions should be provided and monitored.

### Production area

4. Specific provisions should be taken during sampling, weighing, mixing and processing operations of crude plants whenever dust is generated, to facilitate cleaning and to avoid cross-contamination, as for example, dust extraction, dedicated premises, etc.

## DOCUMENTATION

### Specifications for starting materials

5. Apart from the data described in general Code of GMP (chapter 4, point 4.11), specifications for medicinal crude plants should include, as far as possible:

- botanical name (with, if appropriate, the name of the originator of the classification, e.g. Linnaeus);
- details of the source of the plant (country or region of origin and where applicable, cultivation, time of harvesting, collection procedure, possible pesticides used, etc.);
- whether the whole plant or only a part is used;
- when a dried plant is purchased, the drying system should be specified;
- plant description, macro and/or microscopical examination;
- suitable identification tests including, where appropriate, identification tests for known active ingredients, or markers. A reference authentic specimen should be available for identification purposes;
- assay, where appropriate, of constituents of known therapeutic activity or of markers;
- methods suitable to determine possible pesticide contamination and limits accepted;
- tests to determine fungal and/or microbial contamination, including aflatoxins and pest-infestations, and limits accepted;
- tests for toxic metals and for likely contaminants and adulterants;
- tests for foreign materials.

Any treatment used to reduce fungal/microbial contamination or other infestation should be documented. Specifications for such procedures should be available and should include details of process, tests and limits for residues.

### Processing instructions

6. The processing instructions should describe the different operations carried out upon the crude plant such as drying, crushing and sifting, and include drying time and temperatures, and methods used to control fragment or particle size. It should also describe security sieving or other methods of removing foreign materials.

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

## SAMPLING

7. Due to the fact that crude drugs are an aggregate of individual plants and contain an element of heterogeneity, their sampling has to be carried out with special care by personnel with particular expertise. Each batch should be identified by its own documentation.

## QUALITY CONTROL

8. Quality Control personnel should have particular expertise in herbal medicinal products in order to be able to carry out identification tests and recognise adulteration, the presence of fungal growth, infestations, non-uniformity within a delivery of crude plants, etc.

9. The identity and quality of vegetable drug preparations and of finished product should be tested as described below:

   The Control tests on the finished product must be such as to allow the qualitative and quantitative determination of the composition of the active ingredients and a specification has to be given which may be done by using markers if constituents with known therapeutic activity are unknown. In the case of vegetable drugs or vegetable drug preparations with constituents of known therapeutic activity, these constituents must also be specified and quantitatively determined.

   If a herbal remedy contains several vegetable drugs or preparations of several vegetable drugs and it is not possible to perform a quantitative determination of each active ingredient, the determination may be carried out jointly for several active ingredients. The need for this procedure must be justified.

# ANNEX 8

# SAMPLING OF STARTING AND PACKAGING MATERIALS

## PRINCIPLE

Sampling is an important operation in which only a small fraction of a batch is taken. Valid conclusions on the whole cannot be based on tests which have been carried out on non-representative samples. Correct sampling is thus an essential part of a system of Quality Assurance.

Note: Sampling is dealt with in Chapter 6 of the Code, items 6.11 to 6.14. This Annex gives additional directives on the sampling of starting and packaging materials.

## PERSONNEL

1. Personnel who take samples should receive initial and on-going regular training in the disciplines relevant to correct sampling. This training should include:

   - sampling plans,
   - written sampling procedures,
   - the techniques and equipment for sampling,
   - the risks of cross-contamination,
   - the precautions to be taken with regard to unstable and/or sterile substances,
   - the importance of considering the visual appearance of materials, containers and labels,
   - the importance of recording any unexpected or unusual circumstances.

## STARTING MATERIALS

2. The identity of a complete batch of starting materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample. It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material will be incorrectly identified on its label.

3. This validation should take account of at least the following aspects:

   - nature and status of the manufacturer and of the supplier and their understanding of the GMP requirements of the Pharmaceutical Industry;
   - the Quality Assurance system of the manufacturer of the starting material;
   - the manufacturing conditions under which the starting material is produced and controlled;
   - the nature of the starting material and the medicinal products in which it will be used.

   Under such arrangements, it is possible that a validated procedure exempting identity testing of each incoming container of starting material could be accepted for:

   - starting materials coming from a single product manufacturer or plant;
   - starting materials coming directly from a manufacturer or in the manufacturer's sealed container where there is a history of reliability and regular audits of the manufacturer's Quality Assurance system are conducted by the purchaser (the manufacturer of the medicinal products or by an officially accredited body.

   It is improbable that a procedure could be satisfactorily validated for:

   - starting materials supplied by intermediaries such as brokers where the source of manufacture is unknown or not audited;
   - starting materials for use in parenteral products.

4. The quality of a batch of starting materials may be assessed by taking and testing a representative sample. The samples taken for identity testing could be used for this purpose. The number of samples taken for the preparation of a representative sample should be determined statistically and specified in a sampling plan. The number of individual samples which may be blended to form a composite sample should also be defined, taking into account the nature of the material, knowledge of the supplier and the homogeneity of the composite sample.

## PACKAGING MATERIAL

5. The sampling plan for packaging materials should take account of at least the following: the quantity received, the quality required, the nature of the material (e.g. primary packaging materials and/or printed packaging materials), the production methods, and the knowledge of Quality Assurance system of the packaging materials manufacturer based on audits. The number of samples taken should be determined statistically and specified in a sampling plan.

# ANNEX 9

# MANUFACTURE OF LIQUIDS, CREAMS AND OINTMENTS

## PRINCIPLE

Liquids, creams and ointments may be particularly susceptible to microbial and other contamination during manufacture. Therefore special measures must be taken to prevent any contamination.

Note: The manufacture of liquids, creams and ointments must be done in accordance with the GMP described in this Code and with the other supplementary Annexes, where applicable. The present Annex only stress points which are specific to this manufacture.

## PREMISES AND EQUIPMENT

1. The use of closed systems of processing and transfer is recommended in order to protect the product from contamination. Production areas where the products or open clean containers are exposed should normally be effectively ventilated with filtered air.

2. Tanks, containers, pipework and pumps should be designed and installed so that they may be readily cleaned and if necessary sanitised. In particular, equipment design should include a minimum of dead-legs or sites where residues can accumulate and promote microbial proliferation.

3. The use of glass apparatus should be avoided wherever possible. High quality stainless steel is often the material of choice for product contact parts.

## PRODUCTION

4. The chemical and microbiological quality of water used in production should be specified and monitored. Care should be taken in the maintenance of water systems in order to avoid the risk of microbial proliferation. After any chemical sanitization of the water systems, a validated flushing procedure should be followed to ensure that the sanitising agent has been effectively removed.

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

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

7. Materials likely to shed fibres or other contaminants, like cardboard or wooden pallets, should not enter the areas where products or clean containers are exposed.

8. Care should be taken to maintain the homogeneity of mixtures, suspensions, etc. during filling. Mixing and filling processes should be validated. Special care should be taken at the beginning of a filling process, after stoppages and at the end of the process to ensure that homogeneity is maintained.

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

# ANNEX 10

# MANUFACTURE OF PRESSURISED METERED DOSE AEROSOL PREPARATIONS FOR INHALATION

## PRINCIPLE

Manufacture of pressurised aerosol products for inhalation with metering valves requires some special provisions arising from the particular nature of this pharmaceutical form. It should occur under conditions which minimise microbial and particulate contamination. Assurance of the quality of the valve components and, in the case of suspensions, of uniformity is also of particular importance.

Note: The manufacture of metered dose aerosols must be done in accordance with the GMP described in this Code and with the other supplementary Annexes, where applicable. This Annex only stress points which are specific to this manufacture.

## GENERAL

1. There are presently two common manufacturing and filling methods as follows:

   a) Two-shot system (pressure filling). The active ingredient is suspended in a high boiling point propellant, the dose is filled into the container, the valve is crimped on and the lower boiling point propellant is injected through the valve stem to make up the finished product. The suspension of active ingredient in propellant is kept cool to reduce evaporation loss.

   b) One-shot process (cold filling). The active ingredient is suspended in a mixture of propellants and held either under high pressure and/or at a low temperature. The suspension is then filled directly into the container in one shot.

## PREMISES AND EQUIPMENT

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

3. Where products or clean components are exposed, the area should be fed with filtered air, should comply with the requirements of at least a Grade D environment and should be entered through airlocks.

## PRODUCTION AND QUALITY CONTROL

4. Metering valves for aerosols are a more complex engineering article than most pharmaceutical components. Specifications, sampling and testing should be appropriate for this situation. Auditing the Quality Assurance system of the valve manufacturer is of particular importance.

5. All fluids (e.g. liquid or gaseous propellants) should be filtered to remove particles greater than 0.2 micron. An additional filtration where possible immediately before filling is desirable.

6. Containers and valves should be cleaned using a validated procedure appropriate to the use of the product to ensure the absence of any contaminants such as fabrication aids (e.g. lubricants) or undue microbiological contaminants. After cleaning, valves should be kept in clean, closed containers and precautions taken not to introduce contamination during subsequent handling, e.g. taking samples. Containers should be provided to the filling line in a clean condition or cleaned on line immediately before filling.

7. Precautions should be taken to ensure uniformity of suspensions at the point of fill throughout the filling process.

8. When a two-shot filling process is used, it is necessary to ensure that both shots are of the correct weight in order to achieve the correct composition. For this purpose, 100% weight checking at each stage is often desirable.

9. Controls after filling should ensure the absence of undue leakage. Any leakage test should be performed in a way which avoids microbial contamination or residual moisture.

# ANNEX 11

## COMPUTERISED SYSTEMS

## 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 Code. 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.

## PERSONNEL

1. 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.

## VALIDATION

2. 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.

## SYSTEM

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

4. 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.

5. 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.

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

7. 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.

8. 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.

9. 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.

10. 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. 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.

12. For quality auditing purposes, it shall be possible to obtain meaningful printed copies of electronically stored data.

13. Data should be secured by physical or electronic means against wilful or accidental damage, and this in accordance with item 4.9 of the Code. 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.

14. 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.

15. 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.

16. 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.

17. A procedure should be established to record and analyse errors and to enable corrective action to be taken.

18. 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).

19. 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.

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# ANNEX 12

# USE OF IONISING RADIATION IN THE MANUFACTURE OF MEDICINAL PRODUCTS

## INTRODUCTION

Ionising radiation may be used during the manufacturing process for various purposes including the reduction of bioburden and the sterilisation of starting materials, packaging components or products and the treatment of blood products.

There are two types of irradiation process: Gamma irradiation from a radioactive source and high energy Electron irradiation (Beta radiation) from an accelerator.

Gamma irradiation: two different processing modes may be employed:

(i) Batch mode: the products is arranged at fixed locations around the radiation source and cannot be loaded or unloaded while the radiation source is exposed.

(ii) Continuous mode: an automatic system conveys the products into the radiation cell, past the exposed radiation source along a defined path and at an appropriate speed, and out of the cell.

Electron irradiation: the product is conveyed past a continuous or pulsed beam of high energy electrons (Beta radiation) which is scanned back and forth across the product pathway.

## RESPONSIBILITIES

1. Treatment by irradiation may be carried out by the pharmaceutical manufacturer or by an operator of a radiation facility under contract (a "contract manufacturer"), both of whom must hold an appropriate manufacturing authorization.

2. The pharmaceutical manufacturer bears responsibility for the quality of the product including the attainment of the objective of irradiation. The contract operator of the radiation facility bears responsibility for ensuring that the dose of radiation required by the manufacturer is delivered to the irradiation container (i.e. the outermost container in which the products are irradiated).

3. The required dose including justified limits will be stated in the marketing authorization for the product.

## DOSIMETRY

4. Dosimetry is defined as the measurement of the absorbed dose by the use of dosimeters. Both understanding and correct use of the technique is essential for the validation, commissioning and control of the process.

5. The calibration of each batch of routine dosimeters should be traceable to a national or international standard. The period of validity of the calibration should be stated, justified and adhered to.

6. The same instrument should normally be used to establish the calibration curve of the routine dosimeters and to measure the change in their absorbance after irradiation. If a different instrument is used, the absolute absorbance of each instrument should be established.

7. Depending on the type of dosimeter used, due account should be taken of possible causes of inaccuracy including the change in moisture content, change in temperature, time elapsed between irradiation and measurement, and the dose rate.

8. The wavelength of the instrument used to measure the change in absorbance of dosimeters and the instrument used to measure their thickness should be subject to regular checks of calibration at intervals established on the basis of stability, purpose and usage.

## VALIDATION OF THE PROCESS

9. Validation is the action of proving that the process, i.e. the delivery of the intended absorbed dose to the product, will achieve the expected results. The requirements for validation are given more fully in the note for guidance on "the use of ionising radiation in the manufacture of medicinal products".

10. Validation should include dose mapping to establish the distribution of absorbed dose within the irradiation container when packed with product in a defined configuration.

11. An irradiation process specification should include at least the following:

    a) details of the packaging of the product;

    b) the loading pattern(s) of product within the irradiation container. Particular care needs to be taken, when a mixture of products is allowed in the irradiation container, that there is no underdosing of dense product or shadowing of other products by dense product. Each mixed product arrangement must be specified and validated;

    c) the loading pattern of irradiation containers around the source (batch mode) or the pathway through the cell (continuous mode);

    d) maximum and minimum limits of absorbed dose to the product [and associated routine dosimetry];

e) maximum and minimum limits of absorbed dose to the irradiation container and associated routine dosimetry to monitor this absorbed dose;

f) other process parameters, including dose rate, maximum time of exposure, number of exposures, etc.

When irradiation is supplied under contract at least parts (d) and (e) of the irradiation process specification should form part of that contract.

## COMMISSIONING OF THE PLANT

### General

12. Commissioning is the exercise of obtaining and documenting evidence that the irradiation plant will perform consistently within predetermined limits when operated according to the process specification. In the context of this annex, predetermined limits are the maximum and minimum doses designed to be absorbed by the irradiation container. It must not be possible for variations to occur in the operation of the plant which give a dose to the container outside these limits without the knowledge of the operator.

13. Commissioning should include the following elements:

a. Design;

b. Dose mapping;

c. Documentation;

d. Requirement for re-commissioning.

### Gamma irradiators

#### Design

14. The absorbed dose received by a particular part of an irradiation container at any specific point in the irradiator depends primarily on the following factors:

a) the activity and geometry of the source;

b) the distance from source to container;

c) the duration of irradiation controlled by the timer setting or conveyor speed;

d) the composition and density of material, including other products, between the source and the particular part of the container.

15. The total absorbed dose will in addition depend on the path of containers through a continuous irradiator or the loading pattern in a batch irradiator, and on the number of exposure cycles.

16. For a continuous irradiator with a fixed path or a batch irradiator with a fixed loading pattern, and with a given source strength and type of product, the key plant parameter controlled by the operator is conveyor speed or timer setting.

**Dose Mapping**

17. For the dose mapping procedure, the irradiator should be filled with irradiation containers packed with dummy products or a representative product of uniform density. Dosimeters should be placed throughout a minimum of three loaded irradiation containers which are passed through the irradiator, surrounded by similar containers or dummy products. If the product is not uniformly packed, dosimeters should be placed in a larger number of containers.

18. The positioning of dosimeters will depend on the size of the irradiation container. For example, for containers up to 1 x 1 x 0.5 m, a three-dimensional 20 cm grid throughout the container including the outside surfaces might be suitable. If the expected positions of the minimum and maximum dose are known from a previous irradiator performance characterisation, some dosimeters could be removed from regions of average dose and replaced to form a 10 cm grid in the regions of extreme dose.

19. The results of this procedure will give minimum and maximum absorbed doses in the product and on the container surface for a given set of plant parameters, product density and loading pattern.

20. Ideally, reference dosimeters should be used for the dose mapping exercise because of their greater precision. Routine dosimeters are permissible but it is advisable to place reference dosimeters beside them at the expected positions of minimum and maximum dose and at the routine monitoring position in each of the replicate irradiation containers. The observed values of dose will have an associated random uncertainty which can be estimated from the variations in replicate measurements.

21. The minimum observed dose, as measured by the routine dosimeters, necessary to ensure that all irradiation containers receive the minimum required dose will be set in the knowledge of the random variability of the routine dosimeters used.

22. Irradiator parameters should be kept constant, monitored and recorded during dose mapping. The records, together with the dosimetry results and all other records generated, should be retained.

## Electron Beam Irradiators

**Design**

23. The absorbed dose received by a particular portion of an irradiated product depends primarily on the following factors:

    a) the characteristics of the beam, which are: electron energy, average beam current, scan width and scan uniformity;

    b) the conveyor speed;

    c) the product composition and density;

d) the composition, density and thickness of material between the output window and the particular portion of product;

e) the output window to container distance.

24. Key parameters controlled by the operator are the characteristics of the beam and the conveyor speed.

**Dose Mapping**

25. For the dose mapping procedure, dosimeters should be placed between layers of homogeneous absorber sheets making up a dummy product, or between layers of representative products of uniform density, such that at least ten measurements can be made within the maximum range of the electrons. Reference should also be made to sections 18 to 21.

26. Irradiator parameters should be kept constant, monitored and recorded during dose mapping. The records, together with the dosimetry results and all other records generated, should be retained.

**Re-commissioning**

27. Commissioning should be repeated if there is a change to the process or the irradiator which could affect the dose distribution to the irradiation container (e.g. change of source pencils). The extent to re-commissioning depends on the extent of the change in the irradiator or the load that has taken place. If in doubt, re-commission.

## PREMISES

28. Premises should be designed and operated to segregate irradiated from non-irradiated containers to avoid their cross-contamination. Where materials are handled within closed irradiation containers, it may not be necessary to segregate pharmaceutical from non-pharmaceutical materials, provided there is no risk of the former being contaminated by the latter.

Any possibility of contamination of the products by radionuclide from the source must be excluded.

## PROCESSING

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

30. During the process, the radiation dose to the irradiation containers should be monitored using validated dosimetry procedures. The relationship between this dose and the dose absorbed by the product inside the container must have been established during process validation and plant commissioning.

31. Radiation indicators should be used as an aid to differentiating irradiated from non-irradiated containers. They should not be used as the sole means of differentiation or as an indication of satisfactory processing.

32. Processing of mixed loads of containers within the irradiation cell should only be done when it is known from commissioning trials or other evidence that the radiation dose received by individual containers remains within the limits specified.

33. When the required radiation dose is by design given during more than one exposure or passage through the plant, this should be with the agreement of the holder of the marketing authorization and occur within a predetermined time period. Unplanned interruptions during irradiation should be notified to the holder of the marketing authorization if this extends the irradiation process beyond a previously agreed period.

34. Non-irradiated products must be segregated from irradiated products at all times. Methods or doing this include the use of radiation indicators (31.) and appropriate design of premises (28.).

### Gamma irradiators

35. For continuous processing modes, dosimeters should be placed so that at least two are exposed in the irradiation at all times.

36. For batch modes, at least two dosimeters should be exposed in positions related to the minimum dose position.

37. For continuous process modes, there should be a positive indication of the correct position of the source and an interlock between source position and conveyor movement. Conveyor speed should be monitored continuously and recorded.

38. For batch process modes source movement and exposure times for each batch should be monitored and recorded.

39. For a given desired dose, the timer setting or conveyor speed requires adjustment for source decay and source additions. The period of validity of the setting or speed should be recorded and adhered to.

### Electron Beam Irradiators

40. A dosimeter should be placed on every container.

41. There should be continuous recording of average beam current, electron energy, scan-width and conveyor speed. These variables, other than conveyor speed, need to be controlled within the defined limits established during commissioning since they are liable to instantaneous change.

## DOCUMENTATION

42. The numbers of containers received, irradiated and dispatched should be reconciled with each other and with the associated documentation. Any discrepancy should be reported and resolved.

43. The irradiation plant operator should certify in writing the range of doses received by each irradiated container within a batch or delivery.

44. Process and control records for each irradiation batch should be checked and signed by a nominated responsible person and retained. The method and place or retention should be agreed between the plant operator and the holder of the marketing authorization.

45. The documentation associated with the validation and commissioning of the plant should be retained for one year after the expiry date or at least five years after the release of the last product processed by the plant, whichever is the longer.

## MICROBIOLOGICAL MONITORING

46. Microbiological monitoring is the responsibility of the pharmaceutical manufacturer. It may include environmental monitoring where product is manufactured and pre-irradiation monitoring of the product as specified in the marketing authorization.

# ANNEX 13

# MANUFACTURE OF INVESTIGATIONAL MEDICINAL PRODUCTS

## INTRODUCTION

This Annex to the Code was introduced in 1993 so that both those Contracting States instituting controls voluntarily and manufacturers of investigational products would have a reference point to enable common standards to evolve in all contracting States.

Note: The principles and many of the detailed requirements of Good Manufacturing Practice for medicinal products are relevant to the preparation of products for use in clinical trials. This Annex specifically addresses those practices which may be different for investigational products, which are usually not manufactured under a set routine, and with possibly incomplete characterisation of the product at initial stages of clinical development. They also include guidance on ordering, shipping, and returning clinical supplies.

## 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), investigators(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

***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 an investigational product(s) with the object of ascertaining its safety and/or efficacy.

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

***Investigational medicinal product***
A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way

different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

***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.

***Order***
Instruction to process, package and/or ship a certain number of units of investigational product.

***Product specification file***
Reference file containing all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping.

***Shipping/Dispatch***
The operation of packaging for shipment, and sending of ordered medicinal products for clinical trials.

***Sponsor***
An individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

## QUALITY MANAGEMENT

1. Some of the production processes of investigational medicinal products which have no marketing authorization may not be validated to the extent necessary for a routine production. For sterile products, the validation of sterilising processes should be of the same standard as for products authorised for marketing. The product specifications and manufacturing instructions may vary during development. This increased complexity in manufacturing operations requires a highly effective system of Quality Assurance.

2. The Quality Assurance System, designed, set up and verified by the manufacturer, should be described in written procedures maintained by the sponsor, taking into account the GMP principles applied to investigational products.

3. Packaging and labelling operations are often performed after the release of the bulk product and in accordance with specific requirements of different trials. These operations are of paramount importance for the integrity of clinical trials. In this respect, self inspection or independent audits, as referred to in the EU Guideline on Good Clinical Practice and in 9.2. of the Code of GMP are en integral part of the Quality Assurance system.

## PERSONNEL

4. Although it is likely that the number of staff involved will be small, there should be separate people responsible for production and quality control. All production operations should be carried out under control of a clearly identified responsible person. Personnel involved in release of investigational medicinal products should be appropriately trained in quality systems, GMP and regulatory requirements specific to these types of products. They must be independent of the staff responsible for production.

## PREMISES AND EQUIPMENT

5. During manufacture of investigational medicinal products, it may be that different products are handled in the same premises and at the same time, and this reinforces the need to minimise all risks of contamination, including cross-contamination and product mix up, by using appropriate procedures.

6. For the production of the particular products referred to in paragraph 3.6 of the Code of GMP, campaign working may be acceptable in place of dedicated and self-contained facilities. Because the toxicity of the materials may not be fully known, cleaning is of particular importance; account should be taken of the solubility of the product and of excipients in various cleaning solvents.

7. 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. Filling and sealing is often a hand operation presenting great challenges to sterility so enhanced attention should be given to environmental monitoring.

## DOCUMENTATION

8. Specifications (for starting materials, primary packaging materials, intermediate and bulk products and finished products), manufacturing formulae and processing and packaging instructions may be changed as development of the product progresses. Each new version should take into account the latest data, current technology used and the regulatory and pharmacopoeial requirements, and should refer to the previous version to allow traceability to the previous document. Rationales for changes should be recorded.

9. It may not be necessary to produce Master Formula and Processing Instructions, but for every manufacturing operation or supply there should be clear and adequate written instructions and written records. Records are particularly important for the preparation of the final version of the documents to be used in routine manufacture.

10. Batch manufacturing records should be retained for at least two years after completion of the clinical trial or at least two years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

### Order

11. The order may request the processing and/or packaging of a certain number or units and/or their shipping. It may only be given by the sponsor to the manufacturer of an investigational product. 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 it should refer to the approved Product Specification File.

### Product specification file

12. All the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release, storage conditions and/or shipping should be referenced in a Product Specification File. This Product Specification File should be continually updated, ensuring appropriate traceability to the previous versions.

### Manufacturing formulae and processing instructions

13. Any changes should be carried out according to a written procedure which should address any implications for stability and bioequivalence. Changes should be authorised by a responsible person and be clearly recorded.

### Packaging instructions

14. 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 of marketed products when “blinded” labels are used. Supervision procedures such as label reconciliation, line clearance, etc. and the independent checks by quality control staff should accordingly be intensified.

15. Investigational medicinal products must be packed in an individual way for each patient included in the clinical trial. Packaging instructions are based on the order. Contrary to what happens with large-scale manufacturing of licensed medicinal products, batches of investigational medicinal products may be subdivided into different packaging batches and packaged in several operations over a period of time.

16. The number of units to package should be specified prior to the start of the packaging operations, considering also the number of units necessary for carrying out quality controls and the number of samples to be kept. A reconciliation should take place at the end of the packaging and labelling process.

### Labelling instructions

17. Labels should include:

    a) name of the sponsor;

    b) pharmaceutical dosage form, route of administration, quantity of dosage units (and name/identifier of the product and strength/potency in case of open trial);

    c) the batch and/or code number to identify the contents and packaging operation;

d) the trial subject identification number, where applicable;

e) directions for use;

f) “for clinical trial use only”;

g) the name of the investigator (if not included as a code in the trial reference code);

h) a trial reference code allowing identification of the trial site and investigator;

i) the storage conditions;

j) the period of use (use-by date, expiry date or re-test date as applicable), in month/year;

k) “keep out of reach of children” except when the product is for use only in hospital.

The outer packaging may include symbols or pictograms to clarify certain information mentioned above and the request “return empty packaging and unused products”.

Additional information, for example any warnings and handling instructions, where applicable, may be displayed according to the order. A copy of each type of label should be kept in the batch record.

18. On the immediate packaging when the outer packaging carries the particulars mentioned in paragraph 17 a-k, the particulars mentioned in paragraph 17 a-f, shall be given.

19. When the outer packaging carries the particulars mentioned in paragraph 17 a-k and the immediate packaging takes the form of blisterpacks or small immediate packaging units such as ampoules on which the particulars mentioned in paragraph 17 a-f cannot be displayed, the particulars mentioned in paragraph 17 a, c and d as well as route of administration in case of ampoules, shall at least appear on the immediate packaging.

20. In case of use date extension, an additional label should be affixed to the investigational medicinal product. This additional label should include the new use date and repeat the batch number. It may be superposed on the old use date, but, for quality control reasons, not on the original batch number. This operation may be performed on site by the clinical trial monitor(s) or the clinical trial site pharmacist, in accordance with specific and standard operating procedures and under contract if applicable. The operation should be checked by a second person. Documented evidence of this additional labelling should be available in the trial documentation and in the batch records.

## Manufacturing and packaging batch records

21. Manufacturing and packaging batch records should be kept in sufficient detail for the sequence of operations to be accurately traced back. These records should contain any relevant remarks which enhance existing knowledge of the product and allow improvements of the manufacturing operations and justify the procedures used.

# PRODUCTION

## Starting materials

22. The consistency of production may be influenced by quality of the starting materials. Their physical and chemical properties should therefore be defined, documented in their specifications and controlled. Specifications for active starting materials should be as comprehensive as possible, given the current state of knowledge. Specifications for both active and non-active starting materials (excipients) should be periodically re-assessed during development and updated as necessary.

23. Detailed information on the quality of active and non-active starting materials should be available in order to recognise and, as necessary, allow for variation of the production.

## Manufacturing operations

24. During the development phase, validated procedures may not always be available, which makes it difficult to know in advance the critical parameters and the in-process controls that would help to control these parameters. In these cases, provisional production parameters and in-process controls may usually be deduced from experience with analogues. 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.

25. Reconciliation is an essential part of the control of the manufacturing operations. Actual and theoretical yields should be reconciled and any abnormal discrepancy investigated.

26. Where applicable virus inactivation/removal and/or other impurities of biological origin should be no less than for products authorised for marketing. Cleaning procedures should be very stringent and designed in the light of the incomplete knowledge of the toxicity of the investigational product. Where processes such as mixing have not been validated, additional quality control testing may be necessary.

## Principles applicable to comparator product

27. In studies whereby an investigational medicinal product is compared with a marketed product, attention should be paid to ensure the integrity and quality of the comparator product (final dosage form, packaging materials, storage conditions, etc.). If significant changes are to be made to the product, data should be available (e.g. stability, comparative dissolution, bioavailability) to prove that these changes do not significantly alter the original quality characteristics of the product.

28. Because the expiry date stated on the original package has been determined for the medicinal product in that particular package and may not be applicable to the product where it has been repackaged in a different container, it is the responsibility of the sponsor, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the article

may be subjected, to determine a suitable use-by date to be placed on the label. Such date is not later than the expiry date of the original package. In the absence of stability data or if stability is not followed during the clinical trial such date should not exceed 25 % of the remaining time between the date of repackaging and the expiry date on the original manufacturer's bulk container or a six month period from the date the drug is repackaged, whichever is earlier.

### Randomisation code

29. Procedures should describe the generation, distribution, handling and retention of any randomisation code used for packaging investigational products.

### Blinding operations

30. A system should be implemented to allow for a proper identification of the "blinded" products. The system, together with the randomisation code and randomisation list must allow proper identification of the product, including any necessary traceability to the codes and batch number of the product before the blinding operation.

31. Samples of blinded investigational medicinal products should be retained.

## QUALITY CONTROL

32. As processes may not be standardised or fully validated, end product testing takes on more importance to ensure that each batch meets its specification.

33. Quality control should especially pay attention to the compliance with specifications which bear on the efficacy of medicinal products, namely:

- accuracy of the therapeutic or unitary dose: homogeneity, content uniformity;
- release of active substances: solubility, dissolution time, etc.
- estimation of stability, if necessary in accelerated and stress conditions, determination of the preliminary storage conditions and shelf-life of the product.

When necessary, Quality Control should also verify the similarity in appearance, smell and taste of "blinded" medicinal products.

34. Samples of each batch of product should be retained under the responsibility of either the manufacturer or of the importer which released the batch for use in the EU. They should be kept in the primary container used for the study or in a suitable bulk container for at least one year beyond the final shelf-life or two years after completion of the clinical trial whichever is the longest. If the sample is not stored in the pack used for the study, stability data should be available to justify the shelf-life in the pack used.

## RELEASE OF BATCHES

35. Product release is often carried out in two stages, before and after final packaging:

- bulk product assessment: it should cover all relevant factors, including production conditions, results of in-process testing, a review of manufacturing documentation and compliance with the Product specification File and the Order;

- finished product assessment: it should cover, in addition to the bulk product assessment, all relevant factors, including packaging conditions, results of in-process testing, a review of packaging documentation and compliance with the Product Specification File and the Order.

## FREE MOVEMENT

36. Since investigational products are released ("technical green light") by appropriately qualified staff, subsequent analysis after shipping to other Member States is not justified as long as documented evidence is available that appropriate control analysis and product release have taken place in the EEA.

## CONTRACT MANUFACTURE AND CONTRACT ANALYSIS

37. The contract must clearly state, among other provisions, that the medicinal products are to be used in clinical trials. Co-operation between the contracting parties should be very close.

## COMPLAINTS

38. The conclusions of any investigation carried out in relation to a complaint should be discussed between the manufacturer and the sponsor (if different) or between the responsible person of the manufacturer and those responsible for the relevant clinical trial in order to assess any potential impact on the trial and on the product development.

## RECALLS AND RETURNS

39. Procedures for retrieving investigational medicinal products and documenting this retrieval (e.g. for defective products recall, returns after trial completion, expired product return) should be in place. They should be understood by the sponsor, investigator and monitor in addition to the person(s) responsible for recalls.

## SHIPPING - RETURNS - DESTRUCTION

40. Shipping, return and destruction of unused products should be carried out according to written procedures.

### Shipping

41. Shipping of investigational products is conducted according to orders given by the sponsor in the shipping order.

42. Investigational medicinal products are sent to an investigator only after a two step release procedure: the release of the product after quality control ("technical green light") and the authorization to use the product, given by the sponsor ("regulatory green light"). Both releases should be recorded and retained.

43. The packaging must ensure that the 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.

44. The sponsor should ensure that the shipment is to be received in the required conditions and acknowledged by the right addressee.

45. A detailed inventory of the shipments made by the manufacturer should be maintained. It should particularly mention the addressees' identification.

46. Transfers of investigational medicinal products from one trial site to another should remain the exception and only be allowed in case of very expensive product, limited quantity available for clinical trials or in case of emergency. Such transfers should be covered by standard operating procedures which differentiate between the storage location of the product to be transferred (from warehouse under control of the sponsor, from the pharmacy of a trial site, or from the investigator). Should the transferred product have been stored by the investigator, not at the pharmacy, sufficient precautions and controls have to be considered prior to use at an other trial site. In most cases, the product will need to be returned to the sponsor for re-labelling and full finished product specification retesting to ensure that it is still suitable for its intended use and new release.

### Returns

47. Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in written procedures, and approved by authorised staff members.

48. Returned investigational medicinal products should be clearly identified and stored in a dedicated area. Inventory records of the returned medicinal products should be kept.

## Destruction

49. The sponsor is responsible for the destruction of unused investigational medicinal products. Investigational medicinal products should therefore not be destroyed by the manufacturer without prior written authorization by the sponsor.

50. 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. This destruction should be done only after the finalisation of the clinical trial and the compilation of the final report.

51. If the manufacturer is requested to destroy the products, he should deliver a certificate of destruction or a receipt for destruction to the sponsor. These documents should clearly identify the batches and/or patient numbers involved and the actual quantities destroyed.

# [ANNEX 14]

## [MANUFACTURE OF PRODUCTS DERIVED FROM HUMAN BLOOD OR HUMAN PLASMA]Ψ



Ψ This PIC/S Annex is not adopted by the Australian Code of Good Manufacturing Practice for Medicinal Products, 16 August 2002.

# ANNEX 15

# QUALIFICATION AND VALIDATION

## PRINCIPLE

1. This Annex describes the principles of qualification and validation which are applicable to the manufacture of medicinal products. It is a requirement of GMP that manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations. Significant changes to the facilities, the equipment and the processes, which may affect the quality of the product, should be validated. A risk assessment approach should be used to determine the scope and extent of validation.

## PLANNING FOR VALIDATION

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

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

4. The VMP should contain data on at least the following:

   a) validation policy;

   b) organisational structure of validation activities;

   c) summary of facilities, systems, equipment and processes to be validated;

   d) documentation format: the format to be used for protocols and reports;

   e) planning and scheduling;

   f) change control;

   g) reference to existing documents.

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

## DOCUMENTATION

6. A written protocol should be established that specifies how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify critical steps and acceptance criteria.

7. A report that cross-references the qualification and/or validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification.

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

## QUALIFICATION

### Design qualification

9. The first element of the validation of new facilities, systems or equipment could be design qualification (DQ).

10. The compliance of the design with GMP should be demonstrated and documented.

### Installation qualification

11. Installation qualification (IQ) should be performed on new or modified facilities, systems and equipment.

12. IQ should include, but not be limited to the following:

    a) installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;

    b) collection and collation of supplier operating and working instructions and maintenance requirements;

    c) calibration requirements;

    d) verification of materials of construction.

### Operational qualification

13. Operational qualification (OQ) should follow Installation qualification.

14. OQ should include, but not be limited to the following:

    a) tests that have been developed from knowledge of processes, systems and equipment;

    b) tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as “worst case” conditions.

15. The completion of a successful Operational qualification should allow the finalisation of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal "release" of the facilities, systems and equipment.

### Performance qualification

16. Performance qualification (PQ) should follow successful completion of Installation qualification and Operational qualification.

17. PQ should include, but not be limited to the following:

    a) tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment;

    b) tests to include a condition or set of conditions encompassing upper and lower operating limits.

18. Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ.

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

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

## PROCESS VALIDATION

### General

20. The requirements and principles outlined in this chapter are applicable to the manufacture of pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes and re-validation.

21. Process validation should normally be completed prior to the distribution and sale of the medicinal product (prospective validation). In exceptional circumstances, where this is not possible, it may be necessary to validate processes during routine production (concurrent validation). Processes in use for some time should also be validated (retrospective validation).

22. Facilities, systems and equipment to be used should have been qualified and analytical testing methods should be validated. Staff taking part in the validation work should have been appropriately trained.

23. Facilities, systems, equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner.

### Prospective validation

24. Prospective validation should include, but not be limited to the following:

(a) short description of the process;

(b) summary of the critical processing steps to be investigated;

(c) list of the equipment/facilities to be used (including measuring / monitoring / recording equipment) together with its calibration status

(d) finished product specifications for release;

(e) list of analytical methods, as appropriate;

(f) proposed in-process controls with acceptance criteria;

(g) additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;

(h) sampling plan;

(i) methods for recording and evaluating results

(j) functions and responsibilities;

(k) proposed timetable.

25. Using this defined process (including specified components) a series of batches of the final product may be produced under routine conditions. In theory the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, would constitute a validation of the process.

26. Batches made for process validation should be the same size as the intended industrial scale batches.

27. If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise, and (where applicable) the marketing authorisation.

### Concurrent validation

28. In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.

29. The decision to carry out concurrent validation must be justified, documented and approved by authorised personnel.

30. Documentation requirements for concurrent validation are the same as specified for prospective validation.

### Retrospective validation

31. Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.

32. Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.

33. The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance log books, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results.

34. Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.

35. For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches may be examined if justified.

## CLEANING VALIDATION

36. Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure. The rationale for selecting limits of carry over of product residues, cleaning agents and microbial contamination should be logically based on the materials involved. The limits should be achievable and verifiable.

37. Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant.

38. Normally only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to 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.

39. For cleaning procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilising a “worst case” approach can be carried out which takes account of the critical issues.

40. Typically three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.

41. "Test until clean" is not considered an appropriate alternative to cleaning validation.

42. Products which simulate the physicochemical properties of the substances to be removed may exceptionally be used instead of the substances themselves, where such substances are either toxic or hazardous.

## CHANGE CONTROL

43. Written procedures should be in place to describe the actions to be taken if a change is proposed to a starting material, product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or reproducibility of the process. Change control procedures should ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specifications.

44. All changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. The need for, and the extent of, re-qualification and re-validation should be determined.

## REVALIDATION

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

## GLOSSARY

Definitions of terms relating to qualification and validation which are not given in the glossary of the current Code of 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.

***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.

# [ANNEX 16]

## [QUALIFIED PERSON AND BATCH RELEASE]*



* This Annex is specific to the EU GMP Guide and has not been adopted by Australia.

# ANNEX 17

## PARAMETRIC RELEASE

## 1. PRINCIPLE

1.1 The definition of Parametric Release used in this Annex is based on that proposed by the European Organization for Quality: "A system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing process and on the compliance with specific GMP requirements related to Parametric Release."

1.2 Parametric release should comply with the basic requirements of GMP, with applicable annexes and the following guidelines.

## 2. PARAMETRIC RELEASE

2.1 It is recognised that a comprehensive set of in-process tests and controls may provide greater assurance of the finished product meeting specification than finished product testing.

2.2 Parametric release may be authorised for certain specific parameters as an alternative to routine testing of finished products. Authorisation for parametric release should be given, refused or withdrawn jointly by those responsible for assessing products together with the GMP inspectors.

## 3. PARAMETRIC RELEASE FOR STERILE PRODUCTS

3.1 This section is only concerned with that part of Parametric Release which deals with the routine release of finished products without carrying out a sterility test. Elimination of the sterility test is only valid on the basis of successful demonstration that predetermined, validated sterilising conditions have been achieved.

3.2 A sterility test only provides an opportunity to detect a major failure of the sterility assurance system due to statistical limitations of the method.

3.3 Parametric release can be authorised if the data demonstrating correct processing of the batch provides sufficient assurance, on its own, that the process designed and validated to ensure the sterility of the product has been delivered.

3.4 At present Parametric release can only be approved for products terminally sterilized in their final container.

3.5 Sterilization methods according to European Pharmacopoeia requirements using steam, dry heat and ionising radiation may be considered for parametric release.

3.6 It is unlikely that a completely new product would be considered as suitable for Parametric Release because a period of satisfactory sterility test results will form part of the acceptance criteria. There may be cases when a new product is only a minor variation, from the sterility assurance point of view, and existing sterility test data from other products could be considered as relevant.

3.7 A risk analysis of the sterility assurance system focused on an evaluation of releasing non-sterilised products should be performed.

3.8 The manufacturer should have a history of good compliance with GMP.

3.9 The history of non sterility of products and of results of sterility tests carried out on the product in question together with products processed through the same or a similar sterility assurance system should be taken into consideration when evaluating GMP compliance.

3.10 A qualified experienced sterility assurance engineer and a qualified microbiologist should normally be present on the site of production and sterilization.

3.11 The design and original validation of the product should ensure that integrity can be maintained under all relevant conditions.

3.12 The change control system should require review of change by sterility assurance personnel.

3.13 There should be a system to control microbiological contamination in the product before sterilisation.

3.14 There should be no possibility for mix ups between sterilised and non sterilised products. Physical barriers or validated electronic systems may provide such assurance.

3.15 The sterilization records should be checked for compliance to specification by at least two independent systems. These systems may consist of two people or a validated computer system plus a person.

3.16 The following additional items should be confirmed prior to release of each batch of product.

- All planned maintenance and routine checks have been completed in the sterilizer used.
- All repairs and modifications have been approved by the sterility assurance engineer and microbiologist.
- All instrumentation was in calibration.
- The sterilizer had a current validation for the product load processed.

3.17 Once parametric release has been granted, decisions for release or rejection of a batch should be based on the approved specifications. Non-compliance with the specification for parametric release cannot be overruled by a pass of a sterility test.

## 4. GLOSSARY

***Parametric Release***
A system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing process and on the compliance with specific GMP requirements related to Parametric Release.

***Sterility Assurance System***
The sum total of the arrangements made to assure the sterility of products. For terminally sterilized products these typically include the following stages:

a) Product design.

b) Knowledge of and, if possible, control of the microbiological condition of starting materials and process aids (e.g. gases and lubricants).

c) Control of the contamination of the process of manufacture to avoid the ingress of microorganisms and their multiplication in the product. This is usually accomplished by cleaning and sanitization of product contact surfaces, prevention of aerial contamination by handling in clean rooms, use of process control time limits and, if applicable, filtration stages.

d) Prevention of mix up between sterile and non sterile product streams.

e) Maintenance of product integrity.

f) The sterilization process.

g) The totality of the Quality System that contains the Sterility Assurance System e.g. change control, training, written procedures, release checks, planned preventative maintenance, failure mode analysis, prevention of human error, validation calibration, etc.

# [ANNEX 18]

## [GMP GUIDE FOR ACTIVE PHARMACEUTICAL INGREDIENTS] **



** Australia has adopted the ICH GMP Guide for APIs as a Manufacturing Principle.

# GLOSSARY

Definitions given below apply to the words as used in this Code. 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 authority as having the necessary basic scientific and technical background and experience.

***Batch (or lot)***
A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous.

Note: To complete certain stages of manufacture, it may be necessary to divide a batch into a number of subbatches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterised by its intended homogeneity.

For the control of the finished product, a batch of a medicinal products comprises all the units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilisation operation or, in the case of a continuous production process, all the units manufactured in a given period of time.

***Batch number (or lot number)***
A distinctive combination of numbers and/or letters which specifically identifies a batch.

***Biogenerator***
A contained system, such as a fermenter, into which biological agents are introduced along with other materials so as to effect their multiplication or their production of other substances by reaction with the other materials.

Biogenerators are generally fitted with devices for regulation, control, connection, material addition and material withdrawal.

***Biological agents***
Microorganisms, including genetically engineered microorganisms, cell cultures and endoparasites, whether pathogenic or not.

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

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

***Cell bank***
*Cell bank system*: A cell bank system is a system whereby successive batches of a product are manufactured by culture in cells derived from the same master cell bank (fully characterised for identity and absence of contamination). A number of containers from the master cell bank are used to prepare a working cell bank. The cell bank system is validated for a passage level or number of population doublings beyond that achieved during routine production.

*Master cell bank*: A culture of (fully characterised) cells distributed into containers in a single operation, processed together in such a manner as to ensure uniformity and stored in such a manner as to ensure stability. A master cell bank is usually stored at -70°C or lower.

*Working cell bank*: A culture of cells derived from the master cell bank and intended for use in the preparation of production cell cultures. The working cell bank is usually stored at -70°C or lower.

***Cell culture***
The result from the in-vitro growth of cells isolated from multicellular organisms.

***Clean area***
An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

Note: The different degrees of environmental control are defined in 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.

***Code***
This refers to the Australian Code of Good Manufacturing Practice for Medicinal Products, dated 16 August 2002, and includes the supplementary Annexes.

***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 sterilises for the exit of materials and secure operating procedures. In many cases it may add to the effectiveness of primary containment.

***Contained area***
An area constructed and operated in such a manner (and equipped with appropriate air handling and filtration) so as to prevent contamination of the external environment by biological agents from within the area.

***Controlled area***
An area constructed and operated in such a manner that some attempt is made to control the introduction of potential contamination (an air supply approximating to grade D may be appropriate), and the consequences of accidental release of living organisms. The level of control exercised should reflect the nature of the organism employed in the process. At a minimum, the area should be maintained at a pressure negative to the immediate external environment and allow for the efficient removal of small quantities of airborne contaminants.

***Computerised system***
A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.

***Cross contamination***
Contamination of a starting material or of a product with another material or product.

***Crude plant (vegetable drug)***
Fresh or dried medicinal plant or parts thereof.

***Cryogenic vessel***
A container designed to contain liquefied gas at extremely low temperature.

***Cylinder***
A container designed to contain gas at a high pressure.

***Exotic organism***
A biological agent where either the corresponding disease does not exist in a given country or geographical area, or where the disease is the subject of prophylactic measures or an eradication programme undertaken in the given country or geographical area.

***Finished product***
A medicinal 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.

***Liquifiable gases***
Those which, at the normal filling temperature and pressure, remain as a liquid in the cylinder.

***Manifold***
Equipment or apparatus designed to enable one or more gas containers to be filled simultaneously from the same source.

***Manufacture***
All operations of purchase of materials and products, Production, Quality Control, release, storage, distribution of medicinal products and the related controls.

***Manufacturer***
Is a person who manufactures medicial products, being a person who produces the product, or engages in any part of the process of producing the product or of bringing the product to its final state, including engaging in the processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for supply of the product or of any component of ingredient of the product as part of that process.

***Media fill***
Method of evaluating an aseptic process using a microbial growth medium. (Media fills are synonymous to simulated product fills, broth trials, broth fills etc.).

***Medicinal plant***
Plant the whole or part of which is used for pharmaceutical purpose.

***Medicinal products***
Any medicine or similar product intended for human use, which is subject to control under health legislation in the manufacturing or importing State.Packaging
All operations, including filling and labelling, which a bulk product has to undergo in order to become a finished product.

Note: Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not finally packaged, primary containers.

***Packaging material***
Any material employed in the packaging of a medicinal products, 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 products.

***Production***
All operations involved in the preparation of a medicinal products, 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 products 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.

***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 products which may or may not present a quality defect.

***Seed lot***
*Seed lot system*: A seed lot system is a system according to which successive batches of a product are derived from the same master seed lot at a given passage level. For routine production, a working seed lot is prepared from the master seed lot. The final product is derived from the working seed lot and has not undergone more passages from the master seed lot than the vaccine shown in clinical studies to be satisfactory with respect to safety and efficacy. The origin and the passage history of the master seed lot and the working seed lot are recorded.

*Master seed lot*: A culture of a micro-organism distributed from a single bulk into containers in a single operation in such a manner as to ensure uniformity, to prevent contamination and to ensure stability. A master seed lot in liquid form is usually stored at or below -70°C. A freeze-dried master seed lot is stored at a temperature known to ensure stability.

*Working seed lot*: A culture of a micro-organism derived from the master seed lot and intended for use in production. Working seed lots are distributed into containers and stored as described above for master seed lots.

***Specification***
See Chapter 4.

***Starting material***
Any substance used in the production of a medicinal products, but excluding packaging materials.

***Sterility***
Sterility is the absence of living organisms. The conditions of the sterility tests are given in the European or other relevant Pharmacopoeia.[*]

***Supplementary Annexes***
This refers to the Annexes to the Code.

[*] 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.

***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).