

HONG KONG
GOOD MANUFACTURING PRACTICES
GUIDELINES
FOR PHARMACEUTICAL PRODUCTS
1995

PHARMACY AND POISONS BOARD OF HONG KONG

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General considerations

Licensed pharmaceutical products should be manufactured only by licensed manufacturers whose activities are regularly inspected by the Pharmacy and Poison Board. These Good Manufacturing Practices (GMP) guidelines should be used as a standard to justify GMP status which constitutes one of the elements of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce and as a basis for the inspection and licensing of manufacturing facilities.

These guidelines are applicable to all large-scale operations for the production of drugs in their finished dosage forms, including large-scale processes in hospitals and the preparation of clinical trials supplies.

The good practices outlined below are to be considered as general guides. However, they may be adapted to meet individual needs. The equivalence of alternative approaches to quality assurance should be validated. Parts One and Two of these guidelines are not intended to cover the production of active pharmaceutical ingredients for which specific requirements are presented in section 18. Neither do they cover safety aspects for the personnel engaged in manufacture. However, the manufacturer must assure the safety of workers.

Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

Active pharmaceutical ingredient

A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient).

Airlock

An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods.

Authorized person

The person responsible for the release of every batch of finished products for sale.

Batch (or lot)

A defined quantity of starting material, packaging material or product processed in a single process or series of processes so that it could be expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

Batch number (or lot number)

A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificates of analysis, etc.

Batch numbering system

Standard operating procedure (SOP) describing the details of the batch numbering.

Batch records

Include all documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bulk product

Any product that 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 an instrument or system for measuring (especially weighing), recording and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

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.

Consignment (or delivery)

The quantity of a starting material, or of a drug product, made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

Critical process

A process which may cause variation in the quality of the product.

Cross-contamination

Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

Finished product

A product that has undergone all stages of production, including packaging in its final container and labelling.

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 specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate product

Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

Large-volume parenterals

Sterile solutions intended for parenteral application with a volume of 100 ml or more in one container of the finished dosage form.

Manufacture and Manufacturer

These have the same meaning assigned to them under the Pharmacy and Poisons Ordinance.

Master formula

A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Master record

A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Packaging

All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product. Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not the finally packaged, primary container.

Packaging material

Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Pharmaceutical product

This has the same meaning assigned to it under the Pharmacy and Poisons Ordinance.

Processing instructions (See Master formula)***Production***

All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing and packaging, to completion of the finished product.

Quality assurance

See Part One.

Quality control

See Part One.

Quarantine

The status of starting or packaging materials, intermediates, bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

Reconciliation

A comparison, making due allowance for normal variation, between the amount of product or materials theoretically produced or used and the amount actually produced or used.

Recovery (or blending)

The introduction of all or part of previous batches (or of redistilled solvents and similar products) 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.

Returned product

Finished product sent back to the manufacturer.

Specifications

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

Standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material, but of a more general nature (e.g., equipment operation, maintenance and cleaning; cleaning of premises and environmental control; sampling and inspection, etc). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting material

Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

System

A regulated pattern of interacting activities and techniques that are united to form an organized whole.

Validation

The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

Part One

Quality Management in the Drug Industry: Philosophy and Essential Elements

Quality management is defined as the aspect of management function that determines and implements the "quality policy", i.e., the overall intentions and direction of an organization regarding quality, as formally expressed and authorized by top management.

The basic elements of quality management are:

- an appropriate infrastructure or "quality system", encompassing the organizational structure, procedures, processes and resources; and
- systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality. The totality of these actions is termed "quality assurance".

Within an organization, quality assurance serves as a management tool. In contractual situations, quality assurance also serves to generate confidence in the supplier.

In drug manufacture and supply, the terminology may differ. In particular, the term "quality system" is rarely used, and it is "quality assurance" that usually embraces such elements as organizational structure, procedures and processes.

The concepts of quality assurance, good manufacturing practices (GMP) and quality control are interrelated aspects of quality management. They are described here in order to emphasize their relationship and their fundamental importance to the production and control of pharmaceutical products.

Section 1

Quality Assurance

Principle

1. 1. "Quality assurance" is a wide-ranging concept covering all matters which individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of these guidelines such as product design and development.

1.2 The system of quality assurance appropriate to the manufacture of pharmaceutical products should ensure that:

- (a) pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as good laboratory practices (GLP) and good clinical practices (GCP);

- (b) production and control operations are clearly specified in a written form and GMP requirements are adopted;
- (c) managerial responsibilities are clearly specified in job descriptions;
- (d) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
- (e) all necessary controls on starting materials, intermediate products, bulk products and other in-process controls, calibrations and validations are carried out;
- (f) the finished product is correctly processed and checked, according to the defined procedures;
- (g) pharmaceutical products are not sold or supplied before the authorized persons (see also Section 10.6) have certified that each production batch has been produced and controlled in accordance with the requirements of the Pharmacy and Poisons Regulations relevant to the production, control and release of pharmaceutical products;
- (h) satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed and subsequently handled so that their quality is maintained throughout their shelf-life; and
- (i) there is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system.

1.3 The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the Pharmacy and Poisons Regulations 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 of staff in many different departments and at all levels within the company, the company's suppliers and the distributors. To achieve the quality objective reliably, there must be a comprehensively designed and correctly implemented system of quality assurance incorporating GMP and quality control. It should be fully documented and its effectiveness monitored. All parts of the quality assurance system should be appropriately staffed with competent personnel and should have suitable and sufficient premises, equipment and facilities.

Section 2
Good Manufacturing Practices for
Pharmaceutical Products (GMP)

2.1 Good manufacturing practices is that part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use. GMP rules are directed primarily towards diminishing the risks, inherent in any pharmaceutical production, that cannot be prevented completely through the testing of final products. Such risks are essentially of two types: cross-contamination (in particular by unexpected contaminants) and mix-ups (confusion) caused by false labels being put on containers. Under GMP:

- (a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;
- (b) critical steps of manufacturing processes and any significant changes made to the processes are validated;
- (c) all necessary facilities are provided, including:
 - (i) appropriately qualified and trained personnel;
 - (ii) adequate premises and space;
 - (iii) suitable equipment and services;
 - (iv) correct materials, containers and labels;
 - (v) approved procedures and instructions;
 - (vi) suitable storage and transport; and
 - (vii) adequate personnel, laboratories and equipment or in-process controls under the responsibility of the production management;

- (d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;
- (e) operators are trained to carry out procedures correctly;
- (f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected, any significant deviations are fully recorded and investigated;
- (g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
- (h) the proper storage and distribution of the products minimizes any risk to their quality;
- (i) a system is available to recall any batch of product from sale or supply; and
- (j) 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 recurrence.

Section 3

Quality Control

3.1 Quality control is that part of GMP concerned with sampling, specifications and testing and with the organization, 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. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

3.2 Each holder of a manufacturer's licence (except for a holder performing only a fraction of the manufacturing process under a contract - see Section 8) should have a quality control department. The independence of quality control from production is considered fundamental. The quality control department should be independent of other departments and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his or her disposal. Appropriate resources must be available to ensure that all the quality control arrangements are effectively and reliably carried out. The basic requirements for quality control are: -

- (a) adequate facilities, trained personnel and approved procedures must be 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;

- (b) samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department;
- (c) test methods must be validated;
- (d) records must be made (manually and/or by recording instruments) demonstrating that all the required sampling inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated;
- (e) the finished products must contain ingredients complying with the qualitative and quantitative composition of the product; the ingredients must be of the required purity in their proper container and correctly labelled;
- (f) records must be made of the results of inspecting and testing materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;
- (g) no batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the requirements of the Pharmacy and Poisons Regulations; and
- (h) sufficient samples of starting materials and products must be retained to permit future examination of the product if necessary, and that the product is retained in its final pack unless the pack is exceptionally large.

3.3 The quality control department as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, to evaluate, maintain and store the reference standards for substances, to ensure the correct labelling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

3.4 Assessment of finished products should embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product and an examination of the finished pack.

3.5 Quality control personnel must have access to production areas for sampling and investigation as appropriate.

Section 4

Sanitation and Hygiene

4.1 A high level of sanitation and hygiene should be practised in every aspect of the manufacture of pharmaceutical products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene. (For **hygiene**, please refer to Section 10 " Personnel "; and for **sanitation**, Section 11 " Premises ")

Section 5

Validation

5.1 Validation studies are an essential part of GMP and should be conducted in accordance with pre-defined protocols. A written report summarizing recorded results and conclusions should be prepared and stored. Processes and procedures should be established on the basis of a validation study and undergo periodic revalidation to ensure that they remain capable of achieving the intended results. Particular attention should be accorded to the validation of processing, testing and cleaning procedures.

Process Validation

5.2 Critical processes should be validated, prospectively or retrospectively.

5.3 When any new master 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.

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

Section 6

Complaints

Principle

6.1 All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures.

6.2 A person responsible for handling the complaints and deciding the measures to be taken should be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorized person, the latter should be made aware of any complaint, investigation or recall.

6.3 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.

6.4 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.

6.5 If a product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected. In particular, other batches that may contain reprocessed product from the defective batch should be investigated.

6.6 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.

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

6.8 Complaints records should be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.

6.9 The Pharmacy and Poisons Board should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration or any other serious quality problems with a product.

Section 7

Product Recalls

Principle

7.1 There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.

7.2 A person responsible for the execution and coordination of recalls should be designated, as well as sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency. This person should normally be independent of the sales and marketing organization. If this person is different from the authorized person, the latter should be made aware of any recall operation.

7.3 There should be established written procedures, regularly checked and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly at least down to the level of the hospital, the practitioner and the retail outlet.

7.4 All competent authorities of all countries to which a given product may have been distributed should be promptly informed of any intention to recall the product because it is, or is suspected of being, defective.

7.5 The distribution records should be readily available to the person(s) responsible for recalls. They should contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.

7.6 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 product.

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

7.8 An instruction should be included to store recalled products in a secure, segregated area while their fate is decided.

Section 8

Contract Production and Analysis

Principle

8.1 Contract production and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a product or work or analysis of unsatisfactory quality. There must be a written contract between the contract giver and the contract acceptor which clearly establishes the duties of each party. The contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility.

General

8.2 All arrangements for contract manufacture and analysis, including any proposed changes in technical or other arrangements, should be in accordance with the product particulars registered with the Pharmacy and Poisons Board.

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

8.4 The contract should permit the contract giver to audit the facilities of the contract acceptor.

8.5 In the case of contract analysis, the final approval for release must be given by the authorized person(s).

The Contract Giver

8.6 The contract giver is responsible for assessing the competence of the contract acceptor in successfully carrying out the work or tests required and for ensuring by means of the contract that the principles of GMP described in these guidelines are followed.

8.7 The contract giver should provide the contract acceptor with all the information necessary to carry out the contracted operations correctly. The contract giver should ensure that the contract acceptor is fully aware of any problems associated with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials or other products.

8.8 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 product has been released by the authorized person(s).

The Contract Acceptor

8.9 The contract acceptor must have adequate premises, equipment, knowledge, 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 holds a manufacturer's licence.

8.10 The contract acceptor should not pass to a third party any of the work entrusted to him or her 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.

8.11 The contract acceptor should refrain from any activity that may adversely affect the quality of the product manufactured and/or analysed for the contract giver.

The Contract

8.12 A contract should be drawn up between the contract giver and the contract acceptor that 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 GMP. All arrangements for production and analysis must be in accordance with the Pharmacy and Poisons Regulations.

8.13 The contract should specify the way in which the authorized person releasing the batch for sale ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the Pharmacy and Poisons Regulations.

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

8.15 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.

8.16 The contract should describe the handling of starting materials, intermediate and bulk products, and finished products if they are rejected. It should also describe the processing of information if the contract analysis shows that the tested product must be rejected.

Section 9

Self-Inspection and Quality Audits

Principle

9.1 The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely and may, in addition, be performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by pharmacist inspectors appointed by the Pharmacy and Poisons Board is being conducted. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

Items for Self-Inspection

9.2 Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:

- (a) personnel
- (b) premises including personnel facilities
- (c) maintenance of buildings and equipment
- (d) storage of starting materials and finished products
- (e) equipment
- (f) production and in-process controls

- (g) quality control
- (h) documentation
- (i) sanitation and hygiene
- (j) validation and re-validation programmes
- (k) calibration of instruments or measurement systems
- (l) recall procedures
- (m) complaints management
- (n) labels control

Self-Inspection Team

9.3 Management should appoint a self-inspection team from staff who are experts in their own fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of Self-Inspections

9.4 The frequency at which self-inspections are conducted may depend on company requirements.

Self-Inspection Report

9.5 A report should be made at the completion of a self-inspection. The report should include:

- (a) self-inspection results;
- (b) evaluation and conclusions; and
- (c) recommended corrective actions.

Follow-Up Action

9.6 The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality Audit

9.7 It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (see Section 8: "Contract Production and Analysis").

Suppliers' Audits

9.8 The quality control department should have the responsibility, together with other relevant departments, for recommending suppliers who can reliably supply starting and packaging materials.

9.9 Before suppliers are included in the specifications they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it should determine the suppliers' ability to conform with GMP standards for active pharmaceutical ingredients (see Section 18).

Section 10

Personnel

Principle

10.1 The establishment and maintenance of a satisfactory system of quality assurance, the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly understood by the individuals concerned and recorded as written descriptions. All personnel should be aware of the principles of GMP that affect them.

General

10.2 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.

10.3 The manufacturer should have an organization chart. All responsible staff should have their specific duties recorded in written 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 personnel concerned with the application of GMP.

10.4 All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high-quality standards.

10.5 Steps should be taken to prevent unauthorized people from entering production, storage and quality control areas. Personnel who do not work in these areas should not use them as a passageway.

Key Personnel

10.6 Key personnel include the head of production, the head of quality control, the head of sales/distribution and the authorized person(s). Normally, key posts should be occupied by full-time personnel. The heads of production and quality control should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.

10.7 Key personnel responsible for supervising manufacture should have adequate relevant qualifications and practical experience. Similarly, key personnel responsible for supervising quality control should also have adequate relevant qualifications and experience. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of all key personnel should be such as to enable them to exercise independent judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of pharmaceutical products.

10.8 The heads of the production and quality control departments generally have some shared, or jointly exercised, responsibilities relating to quality. These may include:

- (a) the authorization of standard operating procedures (SOPs) documents, including amendments;
- (b) the monitoring and control of the manufacturing environment;
- (c) plant hygiene;
- (d) process validation and calibration of analytical apparatus;
- (e) training, including the application and principles of quality assurance;
- (f) the approval and monitoring of suppliers of materials;
- (g) the approval and monitoring of contract manufacturers;
- (h) the designation and monitoring of storage conditions for materials and products;
- (i) the retention of records;
- (j) the monitoring of compliance with GMP requirements; and
- (k) the inspection, investigation, and taking of samples, in order to monitor factors that may affect product quality.

10.9 The head of the production department generally has the following responsibilities:

- (a) to ensure that products are produced and stored according to the appropriate standard operating procedures (SOPs) in order to obtain the required quality;
- (b) to approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation;

- (c) to ensure that the production records are evaluated and signed by a designated person before they are made available to the quality control department;
- (d) to check the maintenance of the department, premises and equipment;
- (e) to ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available; and
- (f) to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

10.10 The head of the quality control department generally has the following responsibilities:

- (a) to approve or reject starting materials, packaging materials, and intermediate, bulk and finished products;
- (b) to evaluate batch records;
- (c) to ensure that all necessary testing is carried out;
- (d) to approve sampling instructions, specifications, test method and other quality control procedures;
- (e) to approve and monitor analyses carried out under contract;
- (f) to check the maintenance of the department, premises and equipment;
- (g) to ensure that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are done; and
- (h) to ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need.

Other duties of the quality control department are summarized in Section 3.2.

Training

10.11 The manufacturer should provide training in accordance with a written programme 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.

10.12 Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programmes should be available, approved by the head of either production or quality control, as appropriate. Training records should be kept.

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

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

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

Personal Hygiene

10.16 All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.

10.17 All personnel should be trained in the practices of personal hygiene. A high level of personal hygiene should be observed by all those concerned with the manufacturing processes. In particular, personnel should be instructed to wash their hands before entering production areas. Signs to this effect should be posted and instructions observed.

10.18 Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials or drug products until the condition is no longer judged to be a risk.

10.19 All employees should be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment or personnel) that they consider may adversely affect the products.

10.20 Direct contact should be avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product.

10.21 To ensure protection of the product from contamination, personnel should wear clean body and foot coverings appropriate to the duties they perform, including appropriate hair covering. Used clothes, if reusable, should be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.

10.22 Smoking, eating, drinking, chewing, or keeping plants, food, drink, smoking material and personal medicines should not be permitted in production, laboratory and storage areas or in any other areas where they might adversely influence product quality.

10.23 Personal hygiene procedures including the use of protective clothing should apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees e.g. contractors' employees, visitors, senior managers and inspectors.

Section 11

Premises

Principle

11.1 Premises must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to minimize 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.

General

11.2 Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

11.3 Premises used for the manufacture of drug products should be suitably designed and constructed to facilitate good sanitation.

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

11.5 Electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

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

Ancillary Areas

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

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

11.9 Maintenance workshops should if 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.

11.10 Animal houses should be well isolated from other areas, with separate entrances for personnel and animals and with air handling facilities.

Storage Areas

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

11.12 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.

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

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

11.15 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.

11.16 Segregation should be provided for the storage of rejected, recalled or returned materials or products.

11.17 All Part I poisons, antibiotics and dangerous drugs and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.

11.18 Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labelling, and special attention should be paid to the safe and secure storage of these materials.

Weighing Areas (may belong to either storage or production areas)

11.19 The weighing of starting materials and the estimation of yield by weighing should usually be carried out in separate weighing areas designed for that use, for example with provisions for dust control.

Production Area

11.20 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities should, where appropriate, be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g., penicillins) or biological preparations (e.g., live microorganisms). The production of certain other products, such as some antibiotics, hormones, cytotoxic substances, highly active pharmaceutical products and non-pharmaceutical products should not be conducted in the same facilities. The manufacture of technical poisons, such as pesticides and herbicides, should not normally be allowed in premises used for the manufacture of pharmaceutical products. The principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made.

11.21 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.

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

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

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

11.25 Drains should be of adequate size and equipped to prevent back-flow. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.

11.26 Production areas should be effectively ventilated, with air control facilities (including control of temperature and, where necessary, humidity and filtration) appropriate to the products handled, to the operations undertaken and to the external environment. These production areas should be regularly monitored during production and non-production periods to ensure compliance with these afore-mentioned design specifications.

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

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

Quality Control Area

11.29 Quality control laboratories should be separated from production areas. Areas where biological, microbiological or radioisotope test methods are employed should be separated from each other.

11.30 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 and suitable storage space for samples, reference standards (if necessary, with cooling) and records.

11.31 The design of the laboratories should take into account the suitability of construction materials, fumes prevention and ventilation. Separate air handling units and other provisions are needed for biological, microbiological and radioisotope laboratories.

11.32 A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors, or where it is necessary to isolate the instruments.

Section 12 Equipment

Principle

12.1 Equipment must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of equipment must aim to minimize 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.

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

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

12.4 All service pipings and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.

12.5 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated on a scheduled basis.

12.6 Production equipment should be designed, located and maintained to serve its intended purpose.

12.7 Production equipment should be designed so that it can be easily and thoroughly cleaned on a scheduled basis.

12.8 Control laboratory equipment and instruments should be suited to the testing procedures undertaken.

12.9 Washing and cleaning equipment should be chosen and used so as not to be a source of contamination.

12.10 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 an extent that would affect the quality of the product.

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

Section 13

Materials

Principle

13.1 The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (active, auxiliary, packaging). Special attention should be given to the materials as such.

General

13.2 All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.

13.3 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 on a first-in, first-out basis.

Starting Materials

13.4 The purchase of starting materials is an important operation that should involve staff who have particular and thorough knowledge of the products and suppliers.

13.5 Starting materials should be purchased only from suppliers named in the relevant specification and, where possible, directly from the producer. A certificate of analysis from the manufacturer with precise details of the content and origin of these starting materials must be available. It is also 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 between the manufacturer and the supplier.

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

13.7 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.

13.8 Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the quality control department and investigated.

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

13.10 Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:

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

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

13.11 There should be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.

13.12 Only starting materials released by the quality control department and within their shelf-life should be used.

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

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

13.15 Materials dispensed for each batch of the final product should be kept together and conspicuously labelled as such.

Packaging Materials

13.16 The purchase, handling and control of primary and printed packaging materials shall be handled as for starting materials.

13.17 Particular attention should be paid to printed packaging materials. They should be stored in secure conditions so as to exclude the possibility of unauthorized 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 designated personnel following an approved and documented procedure.

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

13.19 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and its disposal recorded.

13.20 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.

Intermediate and Bulk Products

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

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

Finished Products

13.23 Finished products should be held in quarantine until their final release, after which they should be stored as usable stock under conditions established by the manufacturer.

13.24 The evaluation of finished products and the documentation necessary for release of a product for sale are described in Section 16 (Quality Control).

Rejected and Recovered Materials

13.25 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 by authorized personnel and recorded.

13.26 The reprocessing of rejected products should be exceptional. It is permitted only 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 authorized procedure after evaluation of the risks involved. A record should be kept of the reprocessing. A reprocessed batch should be given a new batch number.

13.27 The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture should be authorized 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.

13.28 Additional testing of any finished product that has been reprocessed, or into which a recovered product has been incorporated, should be conducted by the quality control department.

Recalled Products

13.29 Recalled products should be identified and stored separately in a secure area until a decision is taken on their fate. The decision should be made as soon as possible.

Returned Goods

13.30 Products returned from the market should be destroyed unless it is certain that their quality is satisfactory. They may be considered for re-sale, relabelling or bulking with a subsequent batch only after they have been critically assessed by the quality control department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for re-issue or re-use, although basic chemical reprocessing to recover the active ingredient may be possible. Any action taken should be appropriately recorded.

Reagents and Culture Media

13.31 All reagents and culture media should be recorded upon receipt or preparation.

13.32 Reagents made up in the laboratory should be prepared according to written procedures and appropriately labelled. The label should indicate the concentration, standardization factor, shelf-life, re-standardization due date and the storage conditions. The label should be signed and dated by the person preparing the reagent.

13.33 Both positive and negative controls should be applied to verify the suitability of culture media. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

Reference Standards

13.34 Reference standards may be available in the form of official reference standards. Reference standards prepared by the producer should be tested, released and then stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.

13.35 Official reference standards should be used only for the purpose described in the appropriate monograph.

13.36 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization. All in-house reference standards should be based on official reference standards, when available.

13.37 All reference standards should be stored and used in a manner that will not adversely affect their quality.

Waste Materials

13.38 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards.

13.39 Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points and disposed of safely and in a sanitary manner at regular and frequent intervals.

Miscellaneous

13.40 Rodenticides, insecticides, fumigating agents and sanitizing materials should not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials or finished products.

Section 14 Documentation

Principle

14.1 Good documentation is an essential part of the quality assurance system and, as such, should be related to all aspects of GMP. Its aims are to define the specifications for all materials and methods of manufacture and control, to ensure that all personnel concerned with manufacture know what to do and when to do it, to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale, and to provide an audit trail that will permit investigation of the history of any suspected defective batch. The design and use of documents depend upon the manufacturer. In some cases, some or all of the documents described below may be brought together, but they will usually be separate. The important contribution of the documentation system is that it underpins the quality assurance system and, as such, should be related to all aspects of GMP.

General

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

14.3 Documents should be approved, signed and dated by appropriate authorized persons. No document should be changed without authorization.

14.4 Documents should have unambiguous contents: the title, the nature and the 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.

14.5 Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version.

14.6 Where documents require the entry of data, these entries should be clear, legible and indelible. Sufficient space should be provided for such entries.

14.7 Any alteration made to 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.

14.8 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records and associated standard operating procedures should be retained for at least one year after the expiry date of the finished product.

14.9 Data may be recorded by electronic data processing systems or by photographic or other reliable means. Master formulae and detailed standard operating 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 authorized 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 entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs, or other means. It is particularly important that, during the period of retention, the data are readily available.

Documents Required

Labels

14.10 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, etc).

14.11 All finished drug products should be identified by labelling as required by the Pharmacy and Poisons Ordinance.

14.12 For reference standards, the label or accompanying document should indicate concentration, date of manufacture, expiry date, date the closure is first opened, and storage conditions, where appropriate.

Specifications and Testing Procedures

14.13 Testing procedures should be validated in the context of the available facilities and equipment before they are adopted for routine testing.

14.14 There should be appropriately authorized and dated specifications, including tests on identity, content, purity and quality, for starting and packaging materials and finished product. Where appropriate, these should also be available for intermediate or bulk products. Appropriate specifications for water, solvents and reagents (e.g. acids and bases) used in production should be included.

14.15 Each specification should be approved and maintained by the quality control unit. Specifications for starting materials, intermediates, bulk and finished products are referred to in Sections 14.18 to 14.21.

14.16 Periodic revisions of the specifications may be necessary to comply with the latest edition of the appropriate pharmacopoeias.

14.17 Pharmacopoeias, reference standards, reference spectra and other reference materials should be available in the quality control laboratory.

Specifications for Starting and Packaging Materials

14.18 Specifications for starting and primary or printed packaging materials should provide, if applicable, a description of the materials, including:

- (a) the designated name and the internal code reference;
- (b) the reference, if any, to a pharmacopoeial monograph; and
- (c) qualitative and quantitative requirements with acceptance limits.

Depending on the company's practice, other data may be added to the specification, such as:

- (a) the supplier and the original producer of the materials;
- (b) a specimen of printed materials;
- (c) directions for sampling and testing or a reference to procedures;
- (d) storage conditions and precautions; and
- (e) the maximum period of storage before re-examination.

Packaging materials should conform to specifications, with emphasis placed on the compatibility of the materials with the drug product they contain. The materials should be examined for critical and major physical defects as well as for the correctness of identity markings.

14.19 Documents describing testing procedures should state the required frequency for re-assaying each starting material, as determined by its stability.

Specifications for Intermediate and Bulk Products

14.20 Specifications for intermediate and bulk products should be available if these are purchased or dispatched, or if data obtained from intermediate products are used in 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

14.21 Specifications for finished products should include:

- (a) the designated name of the product and the code reference where applicable;
- (b) the designated name(s) of the active ingredient(s);
- (c) the formula or a reference to the formula;
- (d) a description of the dosage form and package details;
- (e) directions for sampling and testing or a reference to standard operating procedures;
- (f) the qualitative and quantitative requirements, with their acceptance limits;
- (g) the storage conditions and precautions, where applicable; and
- (h) the shelf-life.

Master Formulae

14.22 A formally authorized master formula should exist for each product and batch size to be manufactured.

14.23 The master formula should include:

- (a) the name of the product, with a product reference code relating to its specifications;
- (b) description of the dosage 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 that 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;
- (e) a statement of the processing location and the principal equipment to be used;

- (f) the methods, or reference to the methods, to be used for preparing the critical equipment e.g. cleaning (especially after a change in product), assembling, calibrating, sterilizing;
- (g) detailed stepwise processing instructions (e.g., checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
- (h) the instructions for any in-process controls with their limits;
- (i) where necessary, the requirements for storage of the products, including the container, the labelling and any special storage conditions; and
- (j) any special precautions to be observed.

Packaging Instructions

14.24 Formally authorized packaging instructions should exist for each product, pack size and type. These should normally include, or have a reference to:

- (a) the name of the product;
- (b) a description of its pharmaceutical form, strength and method of application 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 for each packaging material;
- (e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;
- (f) special precautions to be observed, including a careful examination of the packaging 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; and
- (h) details of in-process controls with instructions for sampling and acceptance limits.

Batch Processing Records

14.25 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved master formula. The method of preparation of such records should be designed to avoid transcription errors.

14.26 Before any processing begins, a check should be made that the equipment and work stations are clear of previous products, documents or materials not required for the planned process.

14.27 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 by the person responsible for the processing operations:

- (a) the name of the product;
- (b) the number of the batch being manufactured;
- (c) dates and times of commencement, of significant intermediate stages and of completion of production;
- (d) the name of the person responsible for each stage of production;
- (e) the names of the operators in the different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g. weighing);
- (f) the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
- (g) any relevant processing operation or event and the major equipment used;
- (h) the in-process controls performed, the names of the person carrying them out and the results obtained;
- (i) the amount of product obtained at different and pertinent stages of manufacture (yield) together with comments or explanations for significant deviations from the expected yield; and
- (j) notes on special problems including details, with signed authorization for any deviation from the master formula.

Batch Packaging Records

14.28 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 preparing such records should be designed to avoid transcription errors.

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

14.30 During packaging, the following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature: -

- (a) the name of the product, 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, the quantity actually obtained and any reconciliation;
- (b) the date(s) and time(s) of the packaging operations;
- (c) the name of the responsible person carrying out the packaging operation;
- (d) the names of the operators of the different significant steps;
- (e) the checks made 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 and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;
- (g) whenever possible, samples of the printed packaging materials used, including specimens bearing the batch number, expiry date and any additional overprinting;
- (h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person; and
- (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 product obtained to permit an adequate reconciliation.

Standard Operating Procedures (SOPs) and Records

Receipts

14.31 There should be standard operating procedures and records for the receipt of each starting material and each primary or secondary packaging material.

14.32 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) the date of receipt;
- (d) the supplier's name and, if possible, manufacturer's name;
- (e) the manufacturer's batch or reference number;
- (f) the total quantity and number of containers received;
- (g) the batch number assigned after receipt; and
- (h) any relevant comment (e.g. state of the containers).

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

14.34 Standard operating procedures should be available for each instrument and piece of equipment and placed in close proximity to the equipment.

Sampling

14.35 There should be standard operating procedures for sampling which specify the person(s) authorized to take samples.

14.36 The sampling instructions should include:

- (a) the method of sampling and the sampling plan;
- (b) the equipment to be used;
- (c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
- (d) the amount of sample to be taken;
- (e) instructions for any required subdivision of the sample;

- (f) the type of sample container to be used i.e. whether it is for aseptic sampling or for normal sampling; and
- (g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

Batch (Lot) Numbering

14.37 There should be a standard operating procedure describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a unique batch number.

14.38 The standard operating procedures for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.

14.39 The standard operating procedures for batch numbering should assure that the same batch numbers will not be repeatedly used. This also applies to reprocessing.

14.40 Each batch number allocation should be immediately recorded, e.g. in a logbook. The record should include date of allocation, product identity and size of batch.

Testing

14.41 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.

Records of Analysis

14.42 Analysis records should include at least the following data:

- (a) the name of the material or product and, where applicable, dosage form;
- (b) the 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 specifications (limits);
- (e) dates of testing;
- (f) the names of the persons who performed the testing;
- (g) the names of the persons who verified the testing and the calculations, where appropriate; and

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

Others

14.43 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 an authorized person.

14.44 Records should be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.

14.45 Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for:

- (a) equipment assembly and validation;
- (b) analytical apparatus and calibration;
- (c) clearing of work stations and equipment of previous products, maintenance, cleaning and sanitization;
- (d) personnel matters including qualification, training, clothing, hygiene;
- (e) environmental monitoring;
- (f) pest control;
- (g) complaints;
- (h) recalls; and
- (i) returns.

14.46 Logbooks should be kept with major and critical equipment and should be used to record, as appropriate, any validations, calibrations, maintenance, cleaning or repair operations, including dates and the identity of the people who carried these operations out.

14.47 The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.

14.48 There should be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities to be cleaned.

Part Two
Good Practices in Production and Quality Control

Section 15
Production

Principle

15.1 Production operations must follow clearly defined procedures in accordance with the scope of the manufacturer's licence.

General

15.2 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.

15.3 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be approved in writing by a designated person, with the involvement of the quality control department, when appropriate.

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

15.5 Operations on different products should not be carried out simultaneously or consecutively in the same room unless adequate precautions are taken to avoid any significant risk of mix-up or cross contamination.

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

15.7 Access to production premises should be restricted to authorized personnel.

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

15.9 In-process controls are mostly performed within the production area. They should not carry any risk for the quality of the product.

Prevention of Cross-Contamination and Bacterial Contamination in Production

15.10 When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust.

15.11 Contamination of a starting material or of a product by another material or product has to be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays or organisms from materials and products being processed, from residues on equipment, from intruding insects and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, hormones, cytotoxic substances and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time.

15.12 Cross-contamination should be avoided by appropriate technical or organizational measures, for example:

- (a) production either in segregated areas (which may be required for products such as antibiotics, live vaccines, live bacterial preparations and some other biologicals) or by campaign (separation in time) followed by appropriate cleaning;
- (b) providing appropriate airlocks, pressure differentials and air extraction;
- (c) minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
- (d) wearing protective clothing in 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 a "closed system" of production;
- (g) testing for residues; and
- (h) using cleanliness status labels on equipment.

15.13 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to SOPs.

15.14 Production areas where susceptible products are processed should undergo periodic microbiological monitoring.

Processing Operations: Intermediate and Bulk Products

15.15 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, labels or documents not required for the current operation.

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

15.17 Provisions should be implemented to indicate failures of equipment or services (e.g., water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. Production equipment should be cleaned according to detailed written procedures and stored under clean and dry conditions.

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

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

15.20 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 the correct manner.

15.21 Pipes for distilled, deionized and, where appropriate, other water should be sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

15.22 Measuring, weighing, recording and control equipment and instruments should be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments for performing analytical tests should be checked daily or prior to use.

15.23 The date of calibration and servicing and the date when re-calibration is due should be clearly indicated.

15.24 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.

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

Packaging Operations

15.26 When the programme for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or, where feasible, the use of electronic surveillance equipment.

15.27 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. The line clearance should be performed according to an appropriate checklist and recorded.

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

15.29 Normally, filling and sealing should be followed as quickly as possible by labelling. If labelling is delayed, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

15.30 The correct performance of any printing (for example of code numbers or expiry dates) 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 rechecked at regular intervals.

15.31 Special care should be taken when cut labels are used and when overprinting is carried out off-line or in hand-packaging operations. Roll-feed labels are normally preferable to cut labels in helping to avoid mix-ups. On-line verification of all labels by automated electronic means can be helpful in preventing mix-ups. However, checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

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

15.33 On-line control of the product during packaging should include at least checks on:

- (a) the general appearance of the packages;
- (b) whether the packages are complete;
- (c) whether the correct products and packaging materials are used;
- (d) whether any overprinting is correct; and
- (e) where appropriate, the correct functioning of line monitors.

Samples taken away from the packaging line should not be returned

15.34 Products that have been involved in an unusual event during packaging should be reintroduced into the process only after special inspection, investigation and approval by authorized personnel. Detailed records should be kept of this operation.

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

15.36 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.

Section 16

Good Practices in Quality Control

Principle

16.1 Quality control is concerned with sampling, specifications and testing as well as with the organization, 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 to be satisfactory. Quality control is not confined to laboratory operations, but must be involved in all decisions that may concern the quality of the product. The independence of quality control from production is considered fundamental.

Control of Starting Materials and Intermediate, Bulk and Finished Products

16.2 All tests should follow the instructions given in the relevant test procedure for each material or product. The result should be checked by the supervisor before the material or product is released or rejected.

16.3 Samples should be representative of the batches of material from which they are taken in accordance with the approved written procedure (see Section 14.36).

16.4 Sampling should be carried out so as to avoid contamination or other adverse effects on quality. The containers which have been sampled should be marked accordingly and carefully resealed after sampling.

16.5 Care should be taken during sampling to guard against contamination or mix-up of, or by, the material being sampled. All sampling equipment which comes into contact with the material should be clean. Some particularly hazardous or potent materials may require special precautions.

16.6 Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.

16.7 Each sample container should bear a label indicating:

- (a) the name of the sampled material;
- (b) the batch or lot number;
- (c) the number of the container from which the sample has been taken;
- (d) the signature of the person who has taken the sample; and
- (e) the date of sampling.

Test Requirements

Starting and Packaging Materials

16.8 Before releasing a starting or packaging material for use, the quality control manager should ensure that the materials have been tested for conformity with the specifications for identity, strength, purity and other quality parameters.

16.9 An identity test should be conducted on a sample from each container of starting material (see also Section 13. 11).

16.10 With respect to printed packaging materials, each batch (lot) must be examined following its receipt by the manufacturer.

16.11 In lieu of testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results (see Sections 9.8 and 9.9) and through on-site audits of the supplier's capabilities. (This does not affect Section 16.9). Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain the following information:

- (a) identification of the issuing supplier, signature of the competent official and statement of his or her qualifications;
- (b) the name and batch number of the material tested;
- (c) a statement of specifications and methods used; and
- (d) a statement of test results obtained and the date of testing.

In-Process Control

16.12 In-process control records should be maintained and form a part of the batch records (see Section 15.2).

Finished Products

16.13 For each batch of drug product, there should be an appropriate laboratory determination of satisfactory compliance with its finished product specifications prior to release.

16.14 Products failing to meet the established specifications or any other relevant quality criteria should be rejected. Reprocessing may be performed, if feasible, but the reprocessed product should meet all specifications and other quality criteria prior to its acceptance and release.

Production Record Review (often known as Batch Review)

16.15 Production and control records should be reviewed and any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

16.16 Retention samples from each batch of finished product should be kept for at least one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials should be retained for at least one year beyond the expiry date of the corresponding finished product. Other starting materials (other than solvents, gases and water) should be retained for a minimum of two years if their stability allows. Retention samples of materials and products should be of a size sufficient to permit at least two full re-examinations.

Stability Studies

16.17 The quality control department should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.

16.18 The quality control department should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

16.19 A written programme for on-going stability determination should be developed and implemented to include elements such as:

- (a) a complete description of the drug involved in the study;
- (b) the complete testing parameters and methods describing all tests for potency, purity and physical characteristics and documented evidence that these tests reliably indicate stability;
- (c) provision for the inclusion of a sufficient number of batches;
- (d) the testing schedule for each drug;
- (e) provision for special storage conditions;
- (f) provision for adequate sample retention; and
- (g) a summary of all the data generated, including the evaluation and the conclusions of the study.

16.20 Stability should be determined prior to marketing and following any significant changes.

Part Three Supplementary Guidelines

Section 17 Sterile Pharmaceutical Products

Explanation

These guidelines do not take the place of Parts One and Two but only emphasize specific points relating to the manufacture of sterile preparations to minimize the risks of microbiological, particulate and pyrogen contamination.

General

17.1 The production of sterile preparations should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for goods. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air which has passed through filters of an appropriate efficiency.

17.2 The various operations of component (such as containers and closures) preparation, product preparation, filling and sterilization should be carried out in separate areas within the clean area.

17.3 Clean areas for the production of sterile products are classified according to the required characteristics of the air, in grades A, B, C, and D (see Table 1).

1

Table 1: Air classification system for manufacture of sterile products.

Grade	Maximum number of particles permitted per cubic meter		Maximum number of viable microorganisms permitted per cubic meter
A (Laminar air flow work station) B C D	0.5µm – 5µm	>5µm	less than 1 5 100 500
	3500	None	
	3500	None	
	350000	2000	
	3500000	20000	
Notes: - Laminar air flow systems should provide a homogeneous air speed of about 0.30 m/s for vertical flow and about 0.45m/s for horizontal flow. - In order to reach the B, C and D air grades, the number of air changes should generally be higher than 20 per hour in a room with a good air flow pattern and appropriate high-efficiency particulate air filters. - Low values for contaminants are reliable only when a large number of air samples are taken. - The guidance given for the maximum permitted number of particles corresponds approximately to the United States Federal Standard as follows: Class 100 (grades A and B), Class 10 000 (grade C), and Class 100 000 (grade D).			

It may not always be possible to demonstrate conformity with particular air standards at the point of fill when filling is in progress, owing to the generation of particles or droplets from the product itself.

17.4 Each manufacturing operation requires an appropriate air cleanliness level in order to minimize the risks of particulate or microbial contamination of the product or materials being handled. Section 17.5 gives the minimum air grades required for different manufacturing operations. The particulate and microbiological conditions given in Table 1 should be maintained in the zone immediately surrounding the product whenever the product is exposed to the environment. These conditions should be achieved throughout the background environment if no personnel are present in the processing area, and if the standards fall for any reason it should be possible to recover the conditions after a short "clean-up" period.

Manufacture of Sterile Preparations

17.5 Manufacturing operations are here divided into three categories: first, those in which the preparation is sealed in its final container and terminally sterilized; second, those in which the preparation is sterilized by filtration; and third, those in which the preparation can be sterilized neither by filtration nor terminally and consequently must be produced from sterile starting materials in an aseptic way. Selection of area grades as specified in Sections 17.5.1 to 17.5.3 must be determined by the manufacturer on the basis of validation runs (e.g., sterile media fills).

Terminally Sterilized Products

17.5.1 Solutions should generally be prepared in a grade C environment in order to give low microbial and particulate counts, suitable for immediate filtration and sterilization. Solution preparation could be allowed in a grade D environment if additional measures were taken to minimize contamination, such as the use of closed vessels. For parenterals, filling should be done in a laminar air flow work station (grade A) in a grade C environment. The preparation of other sterile products, e.g., ointments, creams, suspensions and emulsions, and filling of containers should generally be done in a grade C environment before terminal sterilization.

Sterile Filtered Products

17.5.2 The handling of starting materials and the preparation of solutions should be done in a grade C environment. These activities could be allowed in a grade D environment if additional measures are taken to minimize contamination, such as the use of closed vessels prior to filtration. After sterile filtration, the product must be handled and dispensed into containers under aseptic conditions in a grade A or B area with a grade B or C background respectively.

Other Sterile Products Prepared from Sterile Starting Materials in an Aseptic Way

17.5.3 The handling of starting materials and all further processing should be done in a grade A or B area with a grade B or C background respectively.

Manufacture of Sterile Preparations

Table 2: Manufacture of sterile preparations

Manufacturing Operations	Clean Areas for Production of Sterile Products
<p>(1) <u>For Terminally Sterilized Products</u></p> <p>a) Preparation of Solutions</p> <ul style="list-style-type: none"> - to give low microbial and particulate counts, suitable for immediate filtration and sterilization - with additional steps to minimize contamination (e.g. use of closed vessels) <p>b) Filling of parenterals</p> <ul style="list-style-type: none"> - at workstation - in environment <p>c) Preparation and filling of other sterile products (eg. ointments, creams, suspensions, emulsions)</p>	<p>Grade C</p> <p>Grade D</p> <p>Grade A Grade C</p> <p>Grade C</p>
<p>(2) <u>For Sterile Filtered Products</u></p> <p>a) Handling of starting materials and preparation of solutions</p> <ul style="list-style-type: none"> - with additional steps to minimize contamination (e.g. use of closed vessels) <p>b) Handling and filling of product after sterile filtration</p>	<p>Grade C</p> <p>Grade D</p> <p>Either Grade A with B background or Grade B with C background</p>

<p>(3) <u>For other Sterile Products Prepared from Sterile Starting Materials in an Aseptic Way</u></p> <p>Handling of starting materials and further processing</p>	<p>Either Grade A with B background or Grade B with C background</p>
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Personnel

17.6 Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes. Inspections and controls should be conducted from outside the areas as far as possible.

17.7 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 supervision.

17.8 Staff who have been engaged in the processing of animal tissue materials or of cultures of microorganisms other than those used in the current manufacturing process should not enter sterile product areas unless rigorous and clearly defined decontamination procedures have been followed.

17.9 High standards of personal hygiene and cleanliness are essential, and personnel involved in the manufacture of sterile preparations should be instructed to report any condition that may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. A designated competent person should decide actions to be taken about personnel who may be introducing undue microbiological hazards.

17.10 Outdoor clothing and footwear should not be brought into the clean areas, and personnel entering the changing rooms should already be clad in standard factory protective garments. Changing and washing should follow a written procedure.

17.11 The clothing and its quality has to be adapted to the process and the working area, and worn in such a way as to protect the product from contamination.

17.12 Wrist watches and jewellery should not be worn in clean areas, and cosmetics which can shed particles should not be used.

17.13 Clothing should be appropriate to the air grade of the area where the personnel will be working. The description of clothing required for each grade is given below:

Grade D:

The hair and, where appropriate, beard should be covered. General protective clothing 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:

The hair and, where appropriate, beard should be covered. A single or two-piece trouser suit, gathered at the wrists and with a high neck and appropriate shoes or overshoes should be worn. The clothing should shed virtually no fibres or particulate matter.

Grade B:

A headgear should totally enclose the hair and, where appropriate, beard; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets; sterilized, non-powdered rubber or plastic gloves and sterilized 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 should retain particles shed by the body.

17.14 For every worker in a grade B room, clean sterilized protective garments should be provided at each work session, or at least once a day if monitoring results justify it. Gloves should be regularly disinfected during operations, and masks and gloves should be changed at least at every working session. The use of disposable clothing may be necessary in certain circumstances.

17.15 Clothing used in clean areas should be laundered or cleaned in such a way that it does not gather additional particulate contaminants which can later be shed. Separate laundry facilities for such clothing are desirable. If fibres are damaged by inappropriate cleaning or sterilization, there may be an increased risk of shedding particles. Washing and sterilization operations should follow standard operating procedures.

Premises

17.16 All premises should as far as possible be designed to avoid the unnecessary entry of personnel. Grade B areas should be designed such that the operations are visible from outside.

17.17 In clean areas, all exposed surfaces should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants where used.

17.18 To reduce the 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 carefully designed to avoid uncleanable recesses; sliding doors are undesirable for this reason.

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

17.20 Pipes and ducts should be installed so that they do not create recesses which are difficult to clean.

17.21 Sinks and drains should be avoided wherever possible and should be excluded from areas where aseptic operations are carried out. Where installed they should be designed, located, and maintained so as to minimize the risks of microbial contamination; they should be fitted with effective, easily cleanable traps with air breaks to prevent back-flow. Any floor channel should be open, easily cleanable and be connected to drains outside the area in a manner which prevents entry of microbial contaminants.

17.22 Changing rooms should be designed as airlocks and used to provide separation of the different stages of changing, so minimizing microbial and particulate contamination of protective clothing. They should be effectively flushed with filtered air. The use of separate changing rooms for entering and leaving clean areas is sometimes desirable. Hand-washing facilities should be provided only in the changing rooms, not in areas where aseptic work is done.

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

17.24 The utilization of absolute-barrier technology and automated systems to minimize human interventions in processing areas can produce significant advantages in ensuring the sterility of manufactured products. When such techniques are used, the recommendations in this section, particularly those relating to air quality and monitoring, still apply, with appropriate interpretation of the terms "work station" and "environment".

Equipment

17.25 A filtered air supply should maintain a positive pressure relative to surrounding areas under all operational conditions and flush the area effectively. Moreover, particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which the product and the cleaned components in contact with it are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified if it becomes necessary to contain materials such as pathogenic, highly toxic, radioactive or live viral or bacterial materials. Decontamination facilities and the treatment of air leaving a clean area may be necessary for some operations.

17.26 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 persons, operations, or machines to zones of higher product risk.

17.27 A warning system should be included to indicate failure in the air supply. An indicator of pressure difference should be fitted between areas where this difference is important and the pressure difference should be regularly recorded.

17.28 Consideration should be given to restricting unnecessary access to critical filling areas, e.g. grade A filling zones, by the use of a physical barrier.

17.29 A conveyor belt should not pass through a partition between a clean area B and a processing area of lower air cleanliness, unless the belt itself is continuously sterilized (e.g., in a sterilizing tunnel).

17.30 Whenever possible, equipment used for processing sterile products should be chosen so that it can be effectively sterilized by steam or dry heat or other methods.

17.31 Equipment fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If the equipment has to be sterilized, it should be resterilized after complete reassembly.

17.32 When equipment maintenance is carried out within the clean area, clean instruments and tools should be used, and the area should be cleaned and disinfected where appropriate before processing recommences, if the required standards of cleanliness and/or asepsis have not been maintained during the maintenance work.

17.33 All equipment, including sterilizers, air-filtration systems, and water treatment systems including stills, should be subject to planned maintenance and validation; its approved use following maintenance work should be documented.

17.34 Water treatment plants should be designed, constructed and maintained so as to ensure the reliable production of water of an appropriate quality. They should not be operated beyond their designed capacity. Water should be produced, stored and distributed in a manner which prevents microbial growth, for example by constant circulation at 80 °C or not more than 4 h.

Sanitation

17.35 The sanitation of clean areas is particularly important. They should be cleaned frequently and thoroughly in accordance with a written programme approved by the quality control department. Where disinfectants are used, more than one type should be employed with periodic alterations. Monitoring should be regularly undertaken in order to detect the emergence of resistant microbial strains. In view of its limited effectiveness, ultraviolet light should not be used as a substitute for chemical disinfection.

17.36 Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should not be stored for long periods unless sterilized. Partly emptied containers should not be topped up.

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

17.38 Clean areas should be monitored at planned intervals during operations by means of microbial counts of air and surfaces; where aseptic operations are performed, monitoring should be frequent to ensure that the environment is within specifications. The results of monitoring should be considered when batches are assessed for approval. Air particulate quality should also be evaluated on a regular basis. Additional monitoring is sometimes desirable even when there are no production operations, e.g., after validation of systems, cleaning and fumigation.

Processing

17.39 Precautions to minimize contamination should be taken during all processing stages including the stages before sterilization.

17.40 Preparations containing live microbiological organisms should not be made or filled into containers in areas used for the processing of other pharmaceutical products; however, vaccines consisting of dead organisms or of bacterial extracts may be filled into containers, after validated inactivation and validated cleaning procedures, in the same premises as other sterile pharmaceutical products.

17.41 The use of microbial growth nutrient media in the simulation of aseptic operations (sterile media fills, "broth fills") is a valuable part of an overall validation of an aseptic process. Where used, they should have the following characteristics:

- (a) they should simulate as closely as possible actual operations, taking into account such factors as complexity of operations, number of personnel working, and length of time;
- (b) the medium or media selected should be capable of growing a wide spectrum of microorganisms, including those that would be expected to be found in the filling environment; and
- (c) they should include a sufficient number of units to give a high degree of assurance that low levels of contamination, if present, would be detected. The target in the simulation should be zero growth and anything above 0.1% of the number of units used in each broth fill trial should be considered unacceptable. Any contamination should be investigated.

Broth fill trials should be repeated at regular intervals and whenever alterations in the premises, equipment or process are sufficient to warrant revalidation.

- 17.42 Care should be taken that validations do not cause hazard to the processes.
- 17.43 Water sources, water treatment equipment and treated water should be monitored regularly for chemicals, endotoxins and other biological contamination to ensure that the water complies with the specifications appropriate to its use. Records should be maintained of the results of the monitoring and of any action taken.
- 17.44 Activities in clean areas, especially when aseptic operations are in progress, should be kept to a minimum, and the 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.
- 17.45 Microbiological contamination of starting materials ("bio-burden") should be minimal and should be monitored before sterilization. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.
- 17.46 The presence of containers and materials liable to generate fibres should be minimized in clean areas and avoided completely when aseptic work is in progress.
- 17.47 Components, bulk product containers and equipment should be handled after the final cleaning process in such a way that they are not recontaminated. The stage of processing of components, bulk product containers and equipment should be properly identified.
- 17.48 The interval between the washing, drying and sterilization of components, bulk product containers and other equipment as well as between sterilization and use should be as short as possible and subject to a time-limit appropriate to the validated storage conditions.
- 17.49 The time between the start of the preparation of a solution and its sterilization or filtration through a bacteria-retaining filter should be as short as possible. A maximum permissible time should be set for each product that takes into account its composition and the prescribed method of storage.
- 17.50 Any gas that is used to purge a solution or blanket a product should pass through a sterilizing filter.
- 17.51 The microbiological contamination of products ("bio-burden") should be minimal prior to sterilization. There should be a working limit on contamination immediately before sterilization which is related to the efficiency of the method to be used and the risk of pyrogens. All solutions, in particular large volume parenterals, should be passed through a microorganism-retaining filter, if possible immediately before the filling process. Where aqueous solutions are held in sealed vessels, any pressure release outlets should be protected e.g. by hydrophobic microbial air filters.

17.52 Components, bulk-product containers, equipment and any other articles required in a clean area where aseptic work is in progress should be sterilized and, wherever possible, passed into the area through double-ended sterilizers sealed into the wall. Other procedures which achieve the same end of not introducing contamination (e.g. triple wrapping) may be acceptable in some circumstances.

17.53 The efficacy of any new processing procedure should be validated, and the validation repeated at regular intervals thereafter, or when any significant change is made in the process or equipment.

Sterilization

17.54 Sterilization can be achieved by moist or dry heat, by ethylene oxide (or other suitable gaseous sterilizing agent), by filtration with subsequent aseptic filling into sterile final containers, or by irradiation with ionizing radiation (but not with ultraviolet radiation unless thoroughly validated). Each method has its particular applications and limitations. Where possible and practicable, heat sterilization is the method of choice.

17.55 All sterilization processes must be validated. Particular attention should be given when the adopted sterilization method is not in accordance with pharmacopoeial standards or when it is used for a preparation which is not a simple aqueous or oily solution.

17.56 Before any sterilization process is adopted, its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be demonstrated. This work should be repeated at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

17.57 Biological indicators should be considered only as an additional method for monitoring the sterilization. If they are used, strict precautions should be taken to avoid transferring microbial contamination from them.

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

Sterilization by Heat

17.59 Each heat sterilization cycle should be recorded by appropriate equipment with suitable accuracy and precision, e.g., on a time/ temperature chart with a suitably large scale. The temperature should be recorded from a probe at the coolest part of the load or loaded chamber, this point having been determined during the validation, and preferably also checked against a second independent temperature probe located at the same position. The chart, or a photocopy of it, should form part of the batch record. Chemical or biological indicators may also be used but should not take the place of physical controls.

17.60 Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time is started. This time must be determined for each type of load to be processed.

17.61 After the high temperature phase of a heat sterilization cycle, precautions should be taken against contamination of a sterilized load during cooling. Any cooling fluid or gas in contact with the product should be sterilized.

Sterilization by Moist Heat

17.62 This method is suitable only for water wettable materials and aqueous solutions. Both temperature and pressure should be used to monitor the process. The temperature recorder should normally be independent of the controller, and there should be an independent temperature indicator, the reading from which is routinely checked against the chart recorder during the sterilization period. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position throughout the sterilization period. There should be regular leak tests on the chamber when a vacuum phase is part of the cycle.

17.63 The items to be sterilized, 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 sterilization. All parts of the load should be in contact with water or saturated steam at the required temperature for the required time.

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

Sterilization by Dry Heat

17.65 The process used for should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. In case air should be supplied, it should be passed through a microorganism-retaining filter. Where this process of sterilization by dry heat is also intended to remove pyrogens, challenge tests using endotoxins would be required as part of the validation.

Sterilization by Radiation

17.66 Radiation sterilization is used mainly for the sterilization of heat sensitive materials and products. Many pharmaceutical 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 an acceptable method for terminal sterilization.

17.67 If radiation sterilization is carried out by an outside contractor, the manufacturer has the responsibility of ensuring that the above requirements are met and that the sterilization process is validated. The responsibilities of the radiation plant operator (e.g., for the right dose) should also be specified.

17.68 During the sterilization procedure the radiation dose should be measured. For this purpose, dosimeters 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 chamber. 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.

17.69 Biological indicators may be used only as an additional control. Radiation-sensitive colour discs may be used to differentiate between packages that have been subjected to irradiation and those that have not. However, they are not indicators of successful sterilization. The information obtained should constitute part of the batch record.

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

17.71 Materials handling procedures should prevent any mix-up between irradiated and non-irradiated materials. Each package should carry a radiation-sensitive indicator to show whether or not it has been subjected to radiation treatment.

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

Sterilization by Ethylene Oxide

17.73 In some cases other gases and fumigants may be used for sterilization. Ethylene oxide should only be used when no other method is practicable. During process validation it should be shown that the gas has 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. These limits should be incorporated into the specifications.

17.74 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.

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

17.76 Each sterilization 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. Biological indicators should be stored and used according to the manufacturer's instructions, and their performance checked by positive controls.

17.77 For each sterilization 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. The pressure and temperature should be recorded throughout the cycle on a chart. The records should form part of the batch record.

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

Filtration of Pharmaceutical Products which Cannot be Sterilized in Their Final Container

17.79 Whenever possible, products should be sterilized in the final container, preferably by heat sterilization. Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size 0.22 micron (or less), or with at least equivalent microorganism retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds, but not all viruses or mycoplasmas. Consideration should then be given to complementing the filtration process with some degree of heat treatment.

17.80 Due to the potential additional risks of the filtration method as compared with other sterilization processes, a double filter layer or second filtration via a further sterilized microorganism-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.

17.81 Fibre-shedding filters should not be used. The use of asbestos-containing filters should be absolutely excluded.

17.82 The integrity of the filter should be checked by an appropriate method such as a bubble point test immediately after each use (it may also be useful to test the filter in this way before use). The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from this should be noted and investigated. Results of these checks should be recorded in the batch record.

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

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

Containers for Sterile Products

17.85 Containers should be closed by appropriately validated methods. Samples should be checked for integrity according to appropriate procedures.

17.86 Containers sealed under vacuum should be sampled and tested for maintenance of that vacuum after an appropriate predetermined period.

17.87 Filled containers of parenteral products should be inspected individually. When the inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should 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. Operators should pass regular eye-sight checks, with spectacles if worn.

Quality Control

17.88 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 interruption of work;
- (b) for products which have been heat sterilized in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.

17.89 The sterility test applied to the finished product should be regarded only as the last in a series of control measures by which sterility is assured and can be interpreted only in conjunction with the environmental and batch processing records.

17.90 Batches failing an initial sterility test should not be released on the basis of a retest unless an investigation into the type of organism found, and into the environmental and batch processing records involved, show that the original test was invalid.

17.91 For injectable products, consideration should be given to monitoring the water and the intermediate and finished product for endotoxins, according to an established pharmacopoeial method that has been validated for each type of product. When a sample fails these monitoring tests, the cause of failure should be investigated and remedial action taken where necessary.

Section 18

Good Manufacturing Practices for Active Pharmaceutical Ingredients (Bulk Drug Substances)

Explanation

Since there are fundamental distinctions between the production of bulk active pharmaceutical ingredients and the formulation of finished pharmaceutical products, the strict application of GMP as set forth in the main part of these guidelines is not always practicable or necessary. The present supplementary guidelines are intended to outline procedures and practices that manufacturers should employ to ensure that the methods, facilities and controls used for the production of active pharmaceutical ingredients are adopted or managed so that such products have the quality and purity appropriate for their use in finished pharmaceutical products.

General Considerations

18.1 In the manufacture of active pharmaceutical ingredients, overall control is essential to ensure high quality. Haphazard operations cannot be permitted in the manufacture of substances that may be used to save life or to restore or promote health.

18.2 Recommended practices for the manufacture of active pharmaceutical ingredients are set out below. Adherence to these practices, complementing the various control tests carried out from the beginning to the end of the production cycle, will contribute substantially to the production of consistently uniform batches of high quality active pharmaceutical ingredients.

18.3 The manufacturer must assume responsibility for the quality of the active pharmaceutical ingredients produced. The manufacturer alone can avoid mistakes and prevent mishaps by exercising adequate care in both production and control procedures. Full evidence of compliance with GMP should be given from the step from which the processes or the starting materials used have a critical influence on the quality of the active pharmaceutical ingredients.

18.4 The good practices outlined below should be considered as general guides. Whenever necessary, they may be adapted to meet individual needs provided the established quality standards of the active pharmaceutical ingredients are still achieved. They are intended to apply to the manufacturing processes (including packaging and labelling) used in the production of active pharmaceutical ingredients.

18.5 Sometimes several firms cooperate in the production (including packaging and labelling) of an active pharmaceutical ingredient. It may also happen that a finished, packed and labelled active pharmaceutical ingredient is repacked and/or relabelled and given a new designation. Since such procedures constitute part of a manufacturing operation, they should be subject to the relevant requirements set out below.

18.6 The practices outlined below are intended to apply to active pharmaceutical ingredients for both human and veterinary preparations.

Personnel

18.7 Each firm should employ personnel with the necessary qualifications and competence for the production and quality control of active pharmaceutical ingredients. There should be an adequate number of staff with appropriate education, technical knowledge and practical experience related to the job they perform.

18.8 The firm should have a defined organization represented in a chart. Individual responsibilities should be laid down as written instructions in an appropriate language so as to ensure that there are no gaps or overlaps. The responsibilities placed on any one individual should not be so extensive as to incur any risk to quality.

18.9 Staff at all levels should be adequately trained for the tasks and responsibilities assigned to them.

18.10 Measures should be taken to ensure that no person affected by a disease in a communicable form such as having open lesions on exposed surfaces of the body or one which will impair performance is engaged in any production step involving direct contact with the active pharmaceutical ingredients.

Premises

18.11 Premises, including areas containing open tanks, should be of suitable construction. They should provide a suitable environment for manufacturing operations and should be adequately adapted to and of a sufficient size for their intended use. The premises should not contribute to actual or potential mix-ups or contamination of the active pharmaceutical ingredients. The arrangement should provide for a logical work flow.

18.12 The production of sterile products, antibiotics, hormones and cytotoxics must be conducted in separate facilities with completely separate air handling systems. Separate facilities can be achieved by means such as containment via closed production systems.

18.13 To maintain hygienic working conditions, the premises should include facilities for changing clothes, washing and toilet purposes as well as for eating, drinking and smoking.

Equipment

18.14 Manufacturing equipment should be designed, constructed, located and maintained in such a way as to:

- (a) be suitable for its intended use;
- (b) facilitate thorough cleaning;
- (c) minimize the risk of contamination of products and containers during production; and

(d) facilitate efficient and, if applicable, validated and reliable operation.

18.15 Production and testing equipment should be cleaned, sterilized when necessary, used and maintained in accordance with written standard operating procedures. Before starting the production of another product, the multipurpose equipment used should be thoroughly cleaned and checked for cleanliness. Appropriate records of such procedures should be maintained.

18.16 If necessary, the equipment used for production and testing should have been shown to be capable of carrying out the intended processes.

18.17 Process monitoring systems should be available where necessary. Measuring, recording and control equipment should be calibrated and checked at suitable intervals by appropriate methods. Appropriate records of such tests should be maintained.

18.18 Defective equipment should be labelled immediately as defective and repaired or removed as soon as possible. Technical maintenance and repair should be documented.

Sanitation

18.19 Written sanitation programmes should be available. These should include validated cleaning procedures for premises and equipment, a quality standard for water, instructions for hygiene when manufacturing and handling goods, instructions relating to the health, hygienic practices and clothing of personnel and the disposal procedures for waste materials and unusable residues.

18.20 These programmes should be implemented and should regularly be brought to the attention of the personnel involved and emphasized during continued staff training.

18.21 Protective garments and other protective items appropriate to the processes being carried out should be worn.

18.22 Eating, smoking and drinking and unhygienic practices should not be permitted in manufacturing areas.

Documentation

Master Formulae

18.23 Written instructions covering each stage of production, storage and quality control should be available and should be updated whenever necessary.

18.24 There should be a master formula setting out in writing the starting materials, detailed production and quality control procedures, the packaging materials and the labelling for each active pharmaceutical ingredient. Wherever possible, the master formula should be prepared for standard batch sizes.

18.25 Competent persons experienced in production and quality control should be responsible for the content and distribution within the firm of instructions and master formulae. These should be duly signed and dated.

18.26 Outdated master formulae should be withdrawn but retained for reference. Copies of the master formula should be prepared in a manner that will eliminate any possibility of transcription error.

18.27 In certain circumstances, for example in the first production runs following pilot development, the master formula might need to be amended. Any amendments must be formally authorized and signed by competent person(s). The amended document should be replaced at the earliest opportunity by a newly prepared master formula.

Batch Documentation

18.28 A batch manufacturing record should be prepared for the production of each batch of intermediate products and of active pharmaceutical ingredients. It should contain the relevant parts of the master formula and should include the following:

- (a) the name of the product or stage, size and number of the batch;
- (b) the dates of the different stages of production;
- (c) production details, including reference to the main equipment used and yields;
- (d) the batch or reference number (or analytical control number), if any, of starting materials used in the production;
- (e) a record of the in-process controls followed and the results obtained;
- (f) details of, and signed authorization for, any deviation from the master formula (any unplanned deviation being subject to investigation in relation to product quality);
- (g) any recovered materials, and procedures applied;
- (h) the names of the operators and signature of the person responsible for the production operations and the date of signature;
- (i) all analytical records relating to the batch, or a reference that will permit their retrieval;
- (j) a decision for the release or rejection of the batch with the date and signature of the person responsible for the decision.

18.29 Where circumstances require the use of contract production and control facilities, this fact should be stated in the batch record.

18.30 Data may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating 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 authorized 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 entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs or other means. It is particularly important that, during the period of retention, the data are readily available.

Retention of Records and Reference Samples

18.31 Records should be kept in such a way that activities concerning the production and quality control of active pharmaceutical ingredients are traceable.

18.32 Records and reference samples of the active pharmaceutical ingredients, and where necessary of intermediate products, should be retained at least one year beyond the expiry date or for a specified period if there is no expiry date.

Production

Processing Procedures

18.33 Processing should be carried out in accordance with the master formula.

18.34 Steps that are critical for the quality of the active pharmaceutical ingredient should be defined and the procedures applied should be validated.

18.35 Processing should be supervised and performed by competent persons.

18.36 During processing, vessels and significant equipment should be unambiguously labelled or identified with the name of the product and the batch number.

18.37 Information on the daily activities in each processing department should be available in addition to the batch documentation.

Starting Materials

18.38 Starting materials should be received, quarantined, sampled, identified, examined for compliance with established specifications, released or rejected, stored, labelled and dispensed in accordance with written instructions.

18.39 Some starting materials may not be tested for compliance because of the hazards involved (e.g., phosphorus pentachloride and dimethyl sulfate). This is acceptable when a batch certificate of analysis is available from the vendor and when there is a reason based on safety or other valid considerations.

Intermediate Products

18.40 Intermediate products should, where necessary, be tested in accordance with the specifications and should be conspicuously labelled/identified and properly stored.

Active Pharmaceutical Ingredients

18.41 Each batch of finished active pharmaceutical ingredient must meet established specifications for quality, purity, identity and potency, including, where applicable, specifications for tests and limits for residues of solvents and other reactants.

18.42 For the production of sterile active pharmaceutical ingredients, Section 17 ("Sterile Pharmaceutical Products") may be applicable to the steps at which the process may have a critical influence on the quality attributes of the finished pharmaceutical product.

Packaging

18.43 Care should be exercised when packaging materials are selected for active pharmaceutical ingredients. The materials should have no detrimental effect on the substance and should give adequate protection against external influences and potential contamination. Suitable written specifications should be available.

18.44 Attention should be directed at all stages to the prevention of packaging errors. Well established procedures must be employed to protect the quality of the product when it is packaged and to ensure that the correct labels are applied to the containers.

18.45 The containers should be conspicuously marked with the following information:

- (a) the name of the product;
- (b) its quality, if specified;
- (c) the quantity of the product;
- (d) the batch number;
- (e) the expiry or retest date, if specified;
- (f) warnings, if required;
- (g) storage conditions, if specified; and
- (h) the names of the manufacturer and the supplier.

Quality Control

18.46 Every manufacturer should have an independent quality control unit, the head of which is directly responsible to the management of the firm. Among its principal duties, the quality control unit should:

- (a) approve:
 - (i) specifications and testing methods for starting materials, packaging materials, active pharmaceutical ingredient and, if required, intermediate product;
 - (ii) sampling procedures;
 - (iii) instructions regarding sanitation and hygiene;
 - (iv) reprocessing procedures for rejected batches or recovered materials; and
 - (v) other instructions related to the quality of the product.
- (b) be responsible for the release or rejection of starting materials, of active pharmaceutical ingredients, of packaging materials and, if required, of intermediate products.
- (c) ensure that the stability of active pharmaceutical ingredients is monitored.
- (d) be responsible for the investigation of complaints related to the quality of active pharmaceutical ingredients.

18.47 Every manufacturer should have access to a control laboratory. The laboratory should be staffed and fully equipped for performing all quality control tests required. The tests should be performed in accordance with written and validated procedures. Instruments should be calibrated to acceptable standards at suitable intervals and reagents should be of appropriate quality.

18.48 Where circumstances require the use of outside laboratories, this fact should be stated in the analytical records.

Stability Testing

18.49 A written stability-testing programme should be established for active pharmaceutical ingredients. Stability-indicating methods should be used.

18.50 Samples should be stored in suitable containers and in simulated market containers at room temperature or the recommended temperature and under stress conditions.

18.51 Expiry dates should be substantiated by appropriate stability testing. However, providing that testing indicates a reasonable shelf-life, e.g., two years or more under anticipated storage conditions, the product can be labelled with an appropriate arbitrary expiry date but should be retested on or before that date.

Self-Inspection and Quality Audits

18.52 In order to maintain strict adherence to GMP and to all manufacturing procedures and prescribed controls, management should designate an expert or a team of experts to conduct regular independent inspections of its overall production and control procedures. Such experts should be as independent as possible in their inspection of production and control procedures.

18.53 Self-inspections and audits (see Section 9) should be recorded.

Storage

18.54 Active pharmaceutical ingredients should be stored under conditions established by the manufacturer on the basis of stability studies.

18.55 Records should be maintained on the distribution of each batch of an active pharmaceutical ingredient in order to facilitate the recall of the batch if necessary, according to written procedures.

Complaints and Defects

18.56 The manufacturer should maintain written instructions for dealing with complaints and defects concerning the quality of active pharmaceutical ingredients.

18.57 All necessary action should be taken promptly, the complaints thoroughly investigated and all facts recorded.

18.58 The manufacturer should have a system to allow review of all products that may have been affected by a repetitive error or a failure in the procedures of the firm.

Rejected Materials

18.59 The manufacturer should maintain written instructions concerning the handling of rejected materials, whether starting materials, intermediate products, packaging materials or active pharmaceutical ingredients. Rejected materials should be conspicuously identified as such and stored in a controlled manner pending destruction, reprocessing or return to the supplier.