GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS (DRAFT)

FOOD AND DRUG ADMINISTRATION
MINISTRY OF PUBLIC HEALTH
THAILAND

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PART I GENERAL PROVISIONS-FOR PHARMACEUTICAL PRODUCTS

1. Introduction

Pharmaceutical products should be manufactured under the requirements of good manufacturing practices by licensed manufacturers (holders of a manufacturing authorization) with the object of ensuring that users will receive efficacious, safe and good quality products.

2. Definition

The definitions given below apply to the terms used in this code.

2.1 Drug

Any substance that defined in the Drugs Act as a drug.

2.2 batch or lot

A defined quantity of any pharmaceutical product produced during a given cycle of manufacture, that is uniform in character and quality.

2.3 batch number or lot number

A designation in numbers or letters, or combination of both that identifies the batch, and that permits the complete history of the batch including all stages of production, control and distribution, to be traced and reviewed.

2.4 control number

A designation in numbers or letters, or combination of both that identifies the quality control of a batch.

2.5 date of manufacture

A date fixed for the individual batch, indicating the starting date of the manufacture

2.6 expiration date or expiry date

A date fixed for each individual batch before which the batch still meets the required standard specifications for quality.

2.7 manufacturer

The holder of manufacturing authorization

2.8 raw materials

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

2.9 packaging materials

Any material used in packaging of a pharmaceutical product, e.g., containers, closures, bags, cartons, labels, inserts, seals, binding materials, adhesives, tapes, etc.

2.10 intermediate product

Any substance or mixture of substances that must undergo further manufacturing steps before it becomes a bulk product.

2.11 bulk product

Any processed material which must, in order to become a finished product, under go to the packaging operation.

2.12 finished product

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

2.13 documentation

All written procedures, instructions and records involved in the manufacture of a pharmaceutical product.

2.14 master formula

A document or set of documents specifying the raw 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 processing instructions, including in-process controls.

2.15 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, validation). Certain SOPs may be used to supplement product- specific master and batch production documentation.

2.16 manufacture or manufacturing

All operations of purchase of materials and products, production, quality control release, storage, shipment of finished products, and the related controls.

2.17 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.

2.18 in-process control

Checks and tests performed during production 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.

2.19 processing

That part of production cycle starting from weighing, compounding of raw materials to become the bulk product.

2.20 packaging

That part of production cycle starting from filling, labelling and packing for distribution.

2.21 theoretical yield

The quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular pharmaceutical product, based upon the quantity of components to be used, in the absence of any lost of error in actual production.

2.22 sterilization

Inactivation or reduction to an acceptable level of all viable organisms which can be effected by moist or dry heat, gas, filtration and ionizing radiation.

2.23 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.

2.24 clean room or clean area

A room or 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.

2.25 air lock

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.

2.26 quality assurance

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, such as product design and development.

2.27 validation

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

2.28 calibration

The set of operations that 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.

2.29 quality control

All measures taken during manufacturing, designed to ensure that the products conform to established specification of identity, strength, purity and other characteristics.

2.30 specification

A document describing in details the requirements of raw materials, packaging materials, intermediate, bulk and finished product.

2.31 representative sample

A sample that consists if a number of units that are drawn based on rational criteria and intended to assure that the sample accurately represents the batch or the total amount of materials being sampled.

2.32 quarantine

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

2.33 released, approved or passed

The status of materials or products which are allowed to be used for processing, packaging or distribution.

2.34 rejected

The status of materials or products which are not allowed to be used for processing, packaging, or distribution.

2.35 sanitation

Hygienic control during production, including personnel, premises, equipment and material handling (from raw materials to finished products)

2.36 research and development

The studies and collecting data of new drugs. These involve the study on physicochemical, toxicological, pharmacological, pharmaceutical and other related properties of drugs, analytical method, including clinical study, product development and stability study.

2.37 recalled products

The products are recalled by the authority or the manufacturer.

2.38 returned products

The products that are sent back to the manufacturer by the customers.

3. Quality management

3.1 Quality management

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 :

3.1.1 quality system encompassing the organizational structure, procedures, processes, and resources;

3.1.2 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"

The concepts of quality assurance, GMP, and quality control are interrelated aspects of quality management.

3.2 Quality assurance

3.2.1 Quality assurance is a wide - ranging concept covering all matters that 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, such as product design and development.

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

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

3.2.2.2 production and control operations are clearly specified in a written form and GMP requirements are adopted;

3.2.2.3 managerial responsibilities are clearly specified in job descriptions;

3.2.2.4 arrangements are made for the manufacture, supply, and use of the correct raw and packaging materials;

3.2.2.5 all necessary controls on raw materials, packaging materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out;

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

3.2.2.7 each production batch is not sold or supplied before the authorized persons have certified;

3.2.2.8 satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed, and subsequently handled so that quality is maintained throughout their shelf-life;

3.2.2.9 there is a procedure for self-inspection that regularly appraises the effectiveness and applicability of the quality assurance system.

3.3 Good manufacturing practices, GMP

That part of quality assurance which ensures that products are consistently manufactured to the quality standards appropriate to their intended use. It is concerned with both production and quality control procedures.

4. Personnel

4.1 General

4.1.1 All personnel should have appropriate education and be aware of the principles of GMP. They should have the capabilities commensurate with their assigned functions, a thorough understanding of their duties, responsibilities and the operations which they perform.

4.1.2 The organization chart of the manufacturer should have specific duties and responsibilities of each level of responsible staff in written descriptions.

4.1.3 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience.

4.2 Key personnel

4.2.1 The heads of production and quality control should be independent of each other.

4.2.2 The heads of production and quality control must be pharmacists and should have practical experience in the manufacture and quality assurance of pharmaceutical products. The manufacturer should have other key personnel, who have studied a relevant science (e.g. chemistry, microbiology, engineering), in charge of production and of quality control. For the production of each certain group of drugs (penicillins, hormones, biologicals, sterile products, cytotoxic drugs, etc.), it must be supervised by a pharmacist.

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

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

4.2.3.2 to approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation;

4.2.3.3 to ensure that the production records are evaluated and signed by a designated person before they are made available to the quality control department;

4.2.3.4 to check the maintenance of the department, premises, and equipment;

4.2.3.5 to ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available;

4.2.3.6 to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

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

4.2.4.1 to approve or reject raw materials, packaging materials, and intermediate, bulk, and finished products;

4.2.4.2 to evaluate batch records;

4.2.4.3 to ensure that all necessary testing is carried out;

4.2.4.4 to approve sampling instructions, specifications, test methods, and other quality control procedures;

4.2.4.5 to check the maintenance of the department, premises and equipment.

4.2.4.6 to ensure that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are done;

4.2.4.7 to ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need.

4.3 Training

4.3.1 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. Training records should be kept.

4.3.2 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.

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

4.3.4 Visitors or untrained personnel should preferably not be taken into the production and quality control areas listed in 4.3.3. 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.

4.4 Personal hygiene

4.4.1 All personnel engaged in the manufacture of the pharmaceutical products should be healthy and should undergo health examinations upon recruitment and during employment at least once a year.

4.4.2 All personnel should be trained in the practices of personal hygiene, especially all those concerned with manufacturing processes.

4.4.3 Personnel should wear clean garments appropriate to the operations to be carried out, including hair covering, mask, glove, as appropriate.

4.4.4 Direct contact should be avoided between the operator's hands and the exposed products.

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

4.4.6 Eating, drinking, chewing, smoking and the storage of food, drink, smoking materials or personal medicines should not be permitted in production, laboratory, and storage areas or in any other areas where they might adversely influence product quality.

5. Premises

5.1 Premises must be located, designed, constructed, adapted and maintained to suit the operations to be carried out. Their layout and design must aim to permit effective cleaning and maintenance in order to avoid contamination, build-up of dust or dirt.

5.2 Premises should

5.2.1 be designed and constructed so as to afford maximum protection against the entry of insects or other animals;

5.2.2 have a smooth interior surface (walls, floors and ceilings) with free from cracks, and should be easily cleaned or disinfected;

5.2.3 be designed to prevent contamination of materials or products in production areas;

5.2.4 have appropriate lighting, ventilation, temperature, humidity and such that they do not adversely affect, either the pharmaceutical products during manufacture and storage, or the accurate functioning of equipment.

5.3 Dedicated facilities must be available for the production of particular pharmaceutical products as required by the authority, such as highly toxic materials (e.g. cytotoxic drug), highly sensitizing materials (e.g. penicillins)

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

5.5 The premises, including production areas, laboratories, storage areas, corridors and external surroundings should be maintained in a clean and tidy condition.

5.6 The building and facilities (e.g. lamp, fan, air-conditioner) should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products.

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

5.8 Facilities for changing and storing clothes and for washing and toilet purposes should be adequate and appropriate for the number of users.

5.9 Storage areas should

5.9.1 provide adequate space and suitable lighting;

5.9.2 be arrange to allow dry, clean, orderly storage of materials and products under appropriate temperature, humidity and ventilation;

5.9.3 be of sufficient capacity to allow orderly storage of raw and packaging materials, bulk and finished products;

5.9.4 provide separate areas for quarantine status, and these areas must be clearly market; any system replacing the physical quarantine should give equivalent security;

5.9.5 provide safe, secure and segregated areas for storage of highly toxic materials, narcotics, and substances presenting special risks of fire and explosion;

5.9.6 provide segregated areas for storage of rejected, recalled, or returned raw and packaging materials or products as appropriate.

5.10 Quality control area

5.10.1 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, including air-handling facilities.

5.10.2 The design of the laboratories should suit the operations to be carried out in them, and take into account the suitability of construction materials, prevention of fumes, and ventilation. There should be adequate suitable storage space for samples, reference standards and records.

5.10.3 A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture, and other external factors.

6. Sanitation

6.1 Premises should be clean, orderly and free from insects and animals.

6.2 There should be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipments and facilities.

6.3 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials ahould be stored in separate, enclosed cupboards. Waste material should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular intervals.

7. Equipment

7.1 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 permit effective cleaning and maintenance in order to avoid contamination, build-up of dust or dirt.

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

7.3 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.

7.4 Installation qualification of a new equipment should be carried out before it is operated.

7.5 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations. They should be calibrated on a scheduled basis and the results should be recorded.

7.6 Production equipment should be cleaned after each use according to written procedures. Suitable washing and cleaning equipment should be provided and used so as not to be a source of contamination.

7.7 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 products.

7.8 Equipment should be maintained at regular intervals. The action taken should be recorded.

7.9 Defective equipment should be removed from production and quality control areas, if they are awaiting for repair, they should be clearly labelled as defective, under repair.

8. Raw materials, packaging materials and other materials

8.1 Raw materials

8.1.1 all incoming materials should be checked to ensure that the consignment corresponds to the order. containers should be cleaned where necessary, labelled and quarantined.

8.1.2 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.

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

8.1.4 Labels on the containers of raw materials should bear the following information:

8.1.4.1 the designated name of the material and the internal code reference where applicable;
8.1.4.2 the batch number given by the supplier and on receipt by the manufacturer, if any;
8.1.4.3 where appropriate, the status of the contents (e.g., on quarantine, on test, released, rejected, etc);
8.1.4.4 where appropriate, an expiry date or a retest date.

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

8.1.6 Only raw materials released by the quality control department and within their shelf-life should be used on a first-in first-out basis.

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

8.1.8 Each dispensed material and its weight or volume should be independently checked and the check recorded. Materials dispensed for each batch of the final product should be dept together and conspicuously labelled as such.

8.1.9 Rejected materials should be clearly marked and stored separately in restricted areas. They should either be returned to the suppliers or destroyed. Whatever action is taken should be approved by authorized presons and recorded.

8.2 Packaging materials

8.2.1 The handling and control of packaging materials shall be as for raw materials.

8.2.2 Printed packaging materials 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 in separate closed containers so as to avoid mix-ups.

8.2.3 All packaging materials to be used should be checked on delivery to the packaging department for quantity, identity, and conformity with the packaging instructions. The check should be recorded and signed by a designated person.

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

8.3 Reagents and culture media

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

8.3.2 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, the date when restandardization is due, and the storage conditions. The label should be signed and dated by the person preparing the reagent.

8.3.3 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.

8.4 Reference standards

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

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

8.4.3 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.

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

9. Production

Production operations must follow clearly defined procedures and production personnel should be well instructed in the details of the processes concerned, with the objective of obtaining products of the requisite quality.

9.1 Processing

9.1.1 Production staff should follow defined processing instructions. Any deviation from instructions should be written approved by authorized persons.

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

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

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

9.1.5 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.

9.1.6 Cross-contamination should be avoided by appropriate measures, for example;

9.1.6.1 providing segregated production facilities for certain products, such as cytotoxic drugs, penicillins as required by the authority;
9.1.6.2 using effective cleaning procedures for production areas and equipment;
9.1.6.3 providing appropriate airlocks or pressure differentials;
9.1.6.4 using effective air filtration system on recirculated air;
9.1.6.5 using a "closed system" of production;
9.1.6.6 using cleanliness status labels on equipment.

9.1.7 The final yield, and any significant intermediate yield, of each production batch should be recorded and checked against the theoretical yield. In the event of significant variation, steps should be taken to prevent release or further processing of the batch until an adequate explaination can be found.

9.2 Packaging

9.2.1 Packaging operations should follow packaging instructions as defined in master formulae. The instructions should be written approved by authorized persons.

9.2.2 Packaging materials should be stored and handled in such a way as to ensure that those relating to different products do not become intermixed. Access to such materials should be restricted to authorized persons, especially the labels should be strictly controlled.

9.2.3 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.

9.2.4 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 and not required for the current operation. The line clearance should be performed according to an appropriate checklist and recorded.

9.2.5 Bulk products and packaging materials should be checked and written approved for use by the quality control department.

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

9.2.7 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.

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

9.2.9 Upon completion of a packaging operation, a conciliation should be made between the amount of used, defected, unused packaging materials and the number of units produced. Any significant or unusual discrepancy should be investigated.

9.2.10 Any unused batch-coded packaging materials should be destroyed and the destruction recorded. Uncoded printed materials should be returned to stock and the return recorded.

9.2.11 All finished products should be identified by labelling that should comply with government regulations and be quarantined until the products are tested and written approved by the quality control department.

10. Quality control

10.1 Quality control is the 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.

10.2 The quality control department must be independent of production and other departments and under the authority of a person with appropriate qualification and experience. Adequate 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 as follows:

10.2.1 Adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing raw materials, packaging materials, and intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes.

10.2.2 Samples of raw materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department.

10.2.3 Test methods must be validated.

10.2.4 Records must be made 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.

10.2.5 The finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container, and correctly labelled.

10.2.6 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.

10.2.7 No batch of product is to be released for sale or supply prior to certification by the authorized person.

10.3 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 finished products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in environmental monitoring.

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

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

11. Good practices in quality control

11.1 Control of raw materials and intermediate, bulk, and finished products

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

11.1.2 Samples should be representative of the batches of material from which they are taken in accordance with the approved written procedure.

11.1.3 Sampling should be carried out so as to avoid contamination or other adverse effects on quality. The containers that have been sampled should be marked accordingly and carefully resealed after sampling. Some particularly hazardous or potent materials may require special precautions.

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

11.1.5 Each sample container should bear a label indicating:

11.1.5.1 the name of the sampled material (and identification code if available);
11.1.5.2 the batch or lot number;
11.1.5.3 the number of the container from which the sample has been taken;
11.1.5.4 the signature of the person who has taken the sample;
11.1.5.5 the date of sampling.

11.2 Test requirements

11.2.1 Raw and packaging materials

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

11.2.1.2 An identity test should be conducted on a sample from each container of raw material.

11.2.1.3 Each batch (lot) of printed packaging materials must be examined following receipt.

11.2.2 In-process control

In-process control records should be maintained and form a part of the batch records.

11.2.3 Finished products

11.2.3.1 For each batch of drug product. there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

11.2.3.2 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.

11.3 Production record review

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.

11.4 Retained sample

11.4.1 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. Sample from each batch of the finished product that is not defined the expiry date should be kept for at least five years after the manufacturing date.

11.4.2 The samples of active raw materials should be retained for at least one year beyond the expiry date of the corresponding finished product.

11.4.3 Retention samples of raw materials and products should be of a size sufficient to permit at least two full re-examination.

11.5 Stability studies

11.5.1 The quality control department should evaluate the quality and stability of finished products and, when necessary, of raw materials and intermediate products.

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

11.5.3 A written programme for ongoing stability determination should be developed and implemented to include elements such as :

11.5.3 1 a complete description of the drug involved in the study;

11.5.3.2 the complete testing parameters and methods describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;

11.5.3.3 provision for the inclusion of a sufficient number of batches;

11.5.3.4 the testing schedule for each drug;

11.5.3.5 provision for special storage conditions and adequate sample retention;

11.5.3.6 a summary of all the data generated, including the evaluation and the conclusions of the study.

11.5.4 Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc.

12. Documentation

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.

12.1 Preparation of documents

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

12.1.2 Documents should have unambiguous contents: the title, nature, and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check.

12.1.3 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.

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

12.1.5 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.

12.1.6 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 5 year.

12.2 Documents required

12.2.1 Labels

12.2.1.1 Labels applied to containers, equipment, or premises should be clear, unambiguous. It is often helpful in addition to the wording on the labels to use colours to indicate status (for example: quarantined, accepted, rejected.)

12.2.1.2 All finished drug products should be identified by labelling, as required by the national legislation, including the additional information as follows;
(1) the expiry date, if any;
(2) the storage conditions, if any;
(3) precautions, if any.

12.2.1.3 For reference standards, the label or accompanying document should indicate the name of the reference standard, concentration, batch number, expiry date (if any), date the closure is first opened, and storage conditions.

12.2.2 Specifications and testing procedures

12.2.2.1 Specifications and testing procedures should be approved, dated, maintained, and revised by the quality control unit.

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

12.2.2.3 There should be appropriately authorized and dated specifications, and tests for raw and packaging materials and finished products; where appropriate, they should also be available for intermediate and bulk products.

12.2.2.4 Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.

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

12.2.3 Specifications for raw materials, intermediate products, bulk products and packaging materials.

12.2.3.1 Documents describing

(1) specifications for raw and packaging materials should include:

(a) the designated name and characteristics;

(b) the reference, if any;

(c) qualitative and quantitative requirements with acceptance limits;

(d) the supplier and the original producer of the materials;

(e) a specimen of printed materials;

(f) directions for sampling and testing, or a reference to procedures;

(g) storage conditions and precautions, if any;

(h) the maximum period of storage before re-examination (for raw materials);

(i) the expiry date, if any.

(2) specifications for intermediate and bulk products should include:

(a) the designated name and characteristics;

(b) qualitative and quantitative requirements with acceptance limits;

(c) directions for sampling and testing, or a reference to procedures;

(d) storage conditions and precautions, if any.

12.2.3.2 The examination of packaging material should emphasize on the compatibility of the material with the drug product it contains. The material should be examined for critical and major physical defects as well as for the correctness of identity markings.

12.2.4 Specifications for finished products

Specifications for finished products should include:

12.2.4.1 the designated name and characteristics of the product;

12.2.4.2 the designated name (s) of the active ingredients (s);

12.2.4.3 the registration number;

12.2.4.4 package details;

12.2.4.5 the qualitative and quantitative requirements, with acceptance limits;

12.2.4.6 directions for sampling and testing or a reference to procedures;

12.2.4.7 the storage conditions and precautions, if any;

12.2.4.8 the expiry date, if any.

12.2.5 Master formulae

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

12.2.5.2 The master formula should include:

(1) the name, characteristics and strength of the product;

(2) a list of all raw materials to be used with the amount of each material, and the pack size;

(3) the principal equipment used;

(4) 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;

(5) an example of the relevant printed packaging materials and specimens, indicating where the batch number, manufacturing date and expiry date of the product have been marked;

(6) detailed stepwise processing instructions, including any special precautions to be observed;

(7) the instructions for any in-process controls;

(8) a statement of the theoretical yield;

(9) a statement of the expected final yield (standard yield);

(10) the specification for raw materials;

(11) the specification for finished products;

(12) the specification for packaging materials;

(13) recommendations and precautions for storage of finished products.

12.2.6 Batch processing records

12.2.6.1 A batch processing record should be prepared for each batch processed. It should be based on the relevant parts of the currently approved master formula.

12.2.6.2 Before any processing begins, a check should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.

12.2.6.3 Each step of processing, records should be completed and signed by the operator 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.

12.2.6.4 During processing, any special problems including details should be noted, with signed authorization for any deviation from the master formula.

12.2.6.5 The batch processing record should include:

(1) the name of the product (and the code reference, where applicable);

(2) the batch number and the manufacturing date;

(3) batch size;

(4) a statement of the theoretical yield;

(5) a statement of the actual yield;

(6) the quantity and control number of each raw material actually used;

(7) the principal equipment used;

(8) cleaning records of equipment;

(9) detailed stepwise processing instructions, including any special precautions to be observed;

(10) dates and times of commencement, of significant steps of production, and of completion of production; including the initials of the operators and the persons who checked each of these operations;

(11) the in-process controls performed, the initials of the persons carrying them out, and the result obtained;

(12) the product yield obtained at different and pertinent stages of manufacture.

12.2.7 Batch packaging records

12.2.7.1 A batch packaging record should be prepared for each batch. It should be based on the relevant parts of the packaging instructions;

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

12.2.7.3 Each step of packaging, records should be completed and signed by the operator at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the packaging operations.

12.2.7.4 During packaging, any special problems including details should be noted, with signed authorization for any deviation from the packaging instructions.

12.2.7.5 The batch packaging record should include:

(1) the name of the product (and the code reference, where applicable);

(2) the batch number;

(3) the date (s) and time (s) of the packaging operations, including the initials of the operators and the supervisors;

(4) the quantity of bulk product to be packed;

(5) the planned quantity of finished product that will be obtained;

(6) the quantity of finished product actually obtained and the product unpacked;

(7) identity of major equipment used (if applicable);

(8) line clearance check before use of the line to assure that all products and materials have been removed from previous operations;

(9) details of the packaging instructions, including any special precautions to be observed;

(10) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls, and the signature of the person performing the check;

(11) samples of the printed packaging materials used, including specimens bearing the batch number, manufacturing date, expiry date (if any);

(12) the quantities and identification of all printed packaging materials issued, used, destroyed or returned to stock;

(13) the quantity of samples taken during and after packaging;

(14) the record of reconciliation of the quantities of packaging materials used and the quantities of product obtained.

12.2.8 Standard operating procedures (SOPs) and records

12.2.8.1 There should be standard operating procedures and records for the receipt of each delivery of raw material and packaging material.

The records of the receipts should include:

(1) the name of the material and the code reference, where applicable;

(2) the date of receipt;

(3) manufacturer's name and the supplier's name, if available;

(4) the manufacturer's batch or reference number;

(5) the expiry date and the retest date (if any);

(6) the total quantity, and number of containers received;

(7) any relevant comment (e.g., state of the containers).

12.2.8.2 There should be standard operating procedures and records for sampling raw materials, packaging materials and finished products as appropriate. The sampling instructions should include:

(1) the method of sampling and the sampling plan;
(2) the sampling area (as necessary);
(3) the equipment to be used;
(4) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
(5) the number and amount of samples to be taken;
(6) the type of sample containers to be used;
(7) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

12.2.8.3 There should be a standard operating procedure and the record describing the details of the batch numbering system, indicating manufacturing date and batch numbering with the objective of ensuring that each batch of intermediate, bulk, or finished product is identified with a specific batch number, and the same batch numbers will not be repeatly used. Batch- number allocation should be immediately recorded. The record should include:

(1) the name, characteristics and strength of the product;
(2) the batch number and date of allocation;
(3) batch size.

12.2.8.4 There should be standard operating procedures and associated records of actions taken as following:
(1) the labelling, quarantine and storage of raw materials, packaging materials and finished products;
(2) the use of major production equipment and validation;

(3) the use of major analytical instruments and calibration;
(4) the maintenance of production equipment and analytical instruments;
(5) cleaning of production equipment and analytical instruments;
(6) cleaning of production areas;
(7) training, clothing and personal hygiene;
(8) environmental control;
(9) pest control;
(10) handling of complaints and adverse drug reaction;
(11) product recalls;
(12) handling of returned products;
(13) handling of rejected materials and products;
(14) stability testing;
(15) self-inspection;
(16) reprocessing;
(17) release of raw materials, packaging materials and finished products;
(18) the alteration of master formulae.

12.2.8.5 There should be analysis records which include the following data:
(1) the name of the material or product;
(2) characteristics and strength;
(3) the batch number, the manufacturer and/or supplier;
(4) references to the relevant specifications and testing procedures;
(5) dates of testing;
(6) analytical data, test results including observations and calculations;
(7) conclusions and the dated initials of the persons who performed the testing;
(8) a clear statement of release or rejection and the dated signature of the responsible person.

13. Validation

Validation studies are an essential part of GMP and should be conducted in accordance with predefined protocols. A written report summerizing recorded results and conclusions should be prepared. 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

13.1 Critical processes should be validated, as appropriate.

13.2 When any new master formula is adopted, step 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.

13.3 Significant amendments to the manufacturing process, including any change in equipment or materials that may affect product quality, should be validated.

14. Self – inspection

Self – inspection means inspection and evaluation process of the manufacturer to ensure that each batch has been manufactured in compliance with GMP.

14.1 There should be a self-inspection team which consist of personnel who can evaluate the implementation of GMP. The members of the team may be appointed from inside or outside the company.

14.2 Written instructions for self-inspection should be established. These should cover the following items:

14.2.1 personnel
14.2.2 premises including personnel facilities
14.2.3 maintenance of buildings and equipment
14.2.4 receiving and storage of raw and packaging materials, intermediate and bulk products, including storage and distribution of finished products.
14.2.5 equipment
14.2.6 production and in-process controls
14.2.7 quality control
14.2.8 documentation
14.2.9 sanitation and hygiene
14.2.10 validation and revalidation programmes
14.2.11 Calibration of instruments or measurement systems
14.2.12 recall procedures
14.2.13 complaints management
14.2.14 labels control
14.2.15 corrective actions taken from the results of previous self-inspections.

14.3 Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, and there should be an effective follow-up programme.

14.4 The self-inspection report should include:
14.4.1 self – inspection result;
14.4.2 evaluation and conclusions;
14.4.3 recommended corrective actions with the time limits set for corrections as appropriate.

15. Product recalls

15.1 There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective. A person responsible for the execution and coordination of recalls should be designated, as well as the distribution records should be readily

available to this person, and they should contain sufficient information on customers.

15.2 Recall operations should be capable of being initiated promptly down to the level of hospitals, clinics and pharmacies. The competent authority should be promptly informed the recall operations as stated in the legislation.

15.3 The product recalls from each of the customer should be recorded, and concluded the delivered and recovered quantities of the products in order to evaluate the effectiveness of the arrangements for recalls. If there is any mistake, it should be noted for improvement of the next arrangement.

15.4 The manufacturer should store recalled products in a secure segregated area and decide promptly how to manage with products.

16. Distribution records

There should be distribution records, which have sufficient information of customers, of each batch of a product in order to facilitate the recall of the batch if necessary.

17. Complaints

17.1 There should be the written handling of all complaints concerning a product defect. A person responsible for handling the complaints should be designated.

17.2 A complaint should be thoroughly investigated and documented.

17.3 The person in quality control department should be involved in the study of such problems.

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

17.5 If the investigation result finds that a defected product will not safe for the consumers, product recall should be taken immediately.

17.6 Complaints records should be regularly reviewed in order to establish prevention and correction measures for recurring problems.

18. Returned products.

18.1 The returned products should be stored in segregated area waiting for assessment by the quality control department.

18.2 A returned product should be examined physical appearance, its history and quality. A consideration should be made to whether the product should be destroyed, reprocessed or returned to inventory.

18.3 Any action taken should be recorded.

PART II SPECIAL PROVISIONS

19. Sterile pharmaceutical products.

19.1 General

19.1.1 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.

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

19.1.3 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).

Table 1
Air classification system for manufacture of sterile products

Grade	Nearest equivalent to US Federal Standard 209 E	Maximum number of particles permitted per m^3		Maximum number of viable microorganisms permitted per m^3
		0.5- 5 um	> 5 um	
A (Laminar-airflow workstation)	100	3,500	none	less than 1
B	100	3,500	none	5
C	10,000	350,000	2,000	100
D	100,000	3,500,000	20,000	500

19.1.4 To obtain air of the required characteristics, it should be noted that:

19.1.4.1 Laminar-airflow systems should provide a homogeneous air speed of about 0.30 m/s for vertical flow and about 0.45 m/s for horizontal flow.

19.1.4.2 In order to reach the B,C, and D air grades, the number of air changes should generally be higher than 20 per hour.

19.1.4.3 Low values for contaminants are reliable only when a large number of air samples are taken.

19.1.4.4 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.

19.1.5 Each manufacturing operation requires an appropriate air cleanliness level in order to minimize the risks of particulate or microbial contamination of the product being handled.

19.2 Manufacture of sterile preparations

Manufacturing operations are divided into 3 categories:

19.2.1 Terminally sterilized products

19.2.1.1 Solutions should generally be prepared in a grade C environment. 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-airflow workstation (grade A) in a grade C environment.

19.2.1.2 The preparation of other sterile products and filling of containers should generally be done in a grade C environment before terminal sterilization.

19.2.2 Sterile filtered products

19.2.2.1 The handling of raw 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 were taken to minimize contamination, such as the use of closed vessels prior to filtration.

19.2.2.2 The filling should be done under aseptic conditions in a grade A or B area with a grade B or C background respectively.

19.2.3 Sterile products prepared from sterile raw materials in an aseptic way.

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

19.3 Personnel

19.3.1 Only the minimum number of personnel required should be present in clean areas; this is particularly important during aseptic processes.

19.3.2 All personnel (including those concerned with cleaning and maintenance) employed in such areas should receive regular training in disciplines relevant to the correct manufacture of sterile products, including reference to hygiene and to the basic elements of microbiology. Each training should be recorded.

19.3.3 When outside staff who have not received such training need to be brought in, particular care should be taken over their supervision.

19.3.4 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 production areas.

19.3.5 High standards of personal hygiene and cleanliness are essential, and personnel involved in the manufacture of sterile preparations should be required to report immediately to their supervisors if they have any apparent illness, e.g. infected skin, diarrhoea, coughs, cold, wounds.

19.3.6 Wrist-watches and jewellery should not be worn in clean areas, and cosmetics that can shed particles should not be used.

19.3.7 Outdoor clothing 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.

19.3.8 The description of clothing required for each grade of clean areas is given below.

19.3.8.1 Grade D: The hair and beard should be covered. Protective clothing and appropriate shoes should be worn.

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

19.3.8.3 Grade B: Headgear should totally enclose the hair, it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets; sterilized 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.

19.3.9 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. 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.

19.3.10 Clothing used in clean areas should be laundered in separate laundry facilities. Washing and sterilization operations should follow standard operating procedures.

19.4 Premises

19.4.1 All premises should as far as possible be designed to avoid the unnecessary entry of supervisory or control personnel. Grade B areas should be designed so that all operations can be observed from outside.

19.4.2 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.

19.4.3 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.

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

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

19.4.6 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 in such a way as to facilitate efficient operation; they should be fitted with effective, easily cleanable traps with air breaks to prevent back-flow. Any floor channel should be open and easily cleanable and be connected to drains outside the area in a manner that prevents ingress of microbial contaminants.

19.4.7 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.

19.4.8 Airlock doors should be arranged so that only one side may be opened at any one time. They should not be opened simultaneously.

19.5 Equipment

19.5.1 A filtered air supply should maintain a positive pressure relative to surrounding areas under all operational conditions and flush the area effectively. The various recommendations regarding pressure differentials may need to be modified if it becomes necessary to contain materials such as 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.

19.5.2 The airflows do not distribute particles from a particle-generating person, operation, or machine to a zone of higher product risk.

19.5.3 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.

19.5.4 Equipment used for processing sterile products should be chosen so that it can be effectively sterilized.

19.5.5 As far as possible equipment fittings and services should be designed and installed so that operations, maintenance, and repairs can be carried out outside the clean area. Equipment that has to be taken apart for maintenance should be resterilized after complete reassembly wherever possible.

19.5.6 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.

19.5.7 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.

19.5.8 Water-treatment plants should be designed, constructed, and maintained so as to ensure the reliable production of water of an appropriate quality. Water should be produced, stored, and distributed in a manner that prevents microbial growth, for example, by constant circulation at 80° C.

19.6 Sanitation

19.6.1 The production area of sterile products should be cleaned frequently 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 to prevent disinfectant resistance. Monitoring should be regularly undertaken. Ultraviolet light should not be used as a substitute for chemical disinfection.

19.6.2 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.

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

19.6.4 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 and the results of monitoring should be recorded. 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.

19.7 Processing

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

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

19.7.3 The sterile media fill is a valuable part of overall validation of an aseptic process. Such trials should have the following characteristics:

19.7.3.1 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.

19.7.3.2 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.

19.7.3.3 They should include a sufficient number of units of production to give a high degree of assurance that low levels of contamination, if present, would be detected. In each broth-fill trial at least 3,000 units of production should be filled. The contamination rate of not more than 0.1% should be acceptable. Broth fills should be carried out at least twice per year, and whenever there is a significant change in the product, premises, equipment or process.

19.7.4 Water sources, water-treatment equipment, and treated water should be monitored regularly for chemicals, biological contamination, and contamination with endotoxins 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.

19.7.5 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 temperature and humidity should be controlled to offer a comfortable working environment.

19.7.6 Microbiological contamination of raw materials should be minimal. Specifications should include requirements for microbiological monitoring, with limits as necessary.

19.7.7 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.

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

19.7.9 The interval between the washing and the subsequent sterilization of components, bulk-product containers, and 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.

19.7.10 The time between the start of the preparation of a solution and its sterilization should be as short as possible. A maximum permissible time should be set for each product.

19.7.11 Any gas that is used to purge a solution or blanket a product should pass through a sterilizing filter.

19.7.12 The microbiological contamination of products ("bioburden") should be minimal prior to sterilization. There should be a working limit on contamination immediately before sterilization. All solutions, in particular large-volume parenterals, should be passed through a microorganism-retaining filter immediately before the filling process.

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

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

19.8 Sterilization

19.8.1 Sterilization can be achieved by moist or dry heat, by ethylene oxide, by filtration, or by ionizing radiation. Each method has its particular applications and limitations. Where possible and practicable, heat sterilization is the method of choice.

19.8.2 All sterilization processes must be validated. Particular attention should be given when the adopted sterilization method is not in accordance with pharmacopoeial standards.

19.8.3 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 least annually. Records should be kept of the results.

19.8.4 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.

19.8.5 There should be a clear means of differentiating products that have not been sterilized from those that 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 to indicate whether or not a batch (or sub-batch) has passed through a sterilization process.

19.9 Sterilization by heat

19.9.1 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 chart should form part of the batch record.

19.9.2 Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time is started.

19.9.3 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.

19.10 Sterilization by moist heat

19.10.1 Sterilization by moist heat is suitable only for water-wettable materials and aqueous solutions. Both temperature and pressure should be used to monitor the process. There should be regular leak tests on the chamber when a vacuum phase is part of the cycle.

19.10.2 The items to be sterilized, other than products in sealed containers, should be wrapped in a material that allows removal of air and penetration of steam but 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.

19.11 Sterilization by dry heat

The process used for sterilization by dry heat should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. If air is 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.

19.12 Sterilization by radiation

19.12.1 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.

19.12.2 If radiation sterilization is carried out by an outside contractor, the manufacturer has the responsibility of ensuring that this method is suitable for the product, and that the sterilization process is validated. The responsibilities of the radiation plant operator should also be specified.

19.12.3 During the sterilization procedure the radiation dose should be measured. For this purpose, dosimeters that 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. 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.

19.12.4 Validation procedures should ensure that consideration is given to the effect of variations in the density of the packages.

19.12.5 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. A radiation-sensitive indicator is not an indicator of successful sterilization.

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

19.13 Sterilization by ethylene oxide

19.13.1 Ethylene oxide should be used for sterilization only 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.

19.13.2 Direct contact between gas and microbial cells is essential; precautions should be taken to avoid the presence of organisms likely to be enclosed in material such as crystals or dried protein. The nature and quantity of packaging materials can significantly affect the process.

19.13.3 Before exposure to the gas, materials should be brought into equilibrium with the humidity and temperature required by the process.

19.13.4 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.

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

19.13.6 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.

19.13.7 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.

19.14 Sterilization by filtration

19.14.1 Sterilization by filtration should not be used when sterilization by heat is practicable. Solutions or liquids can be sterilized by filtration through a sterile filter of nominal pore size of 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.

19.14.2 Owing 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 should be carried out.

19.14.3 Filters that shed fibres should not be used. The use of asbestos-containing filters should be absolutely excluded.

19.14.4 The integrity of the filter should be checked by an appropriate method such as a bubble point test immediately before and after each use. Results of these checks should be recorded in the batch record.

19.14.5 The same filter should not be used for more than one working day.

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

19.15 Finishing of sterile products

19.15.1 Containers should be closed by appropriately validated methods.

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

19.15.3 Filled containers of parenteral products should be inspected individually. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eyesight checks and be allowed frequent breaks from inspection. Where the automatic method of inspection is used, the effectiveness of the equipment should be validated at intervals.

19.16 Quality control

19.16.1 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, for example:

19.16.1.1 for products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant interruption of work;

19.16.1.2 for products that have been heat sterilized in their final containers, consideration should be given to taking samples from the potentially coolest part of the load.

19.16.2 Batches failing an initial sterility test should not be released on the basis of a second test 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.

19.16.3 Sterility testing method should be validated.

19.16.4 For injectable products, consideration should be given to monitoring the water and the intermediate and finished product for endotoxins as appropriate, using an established pharmacopoeial method. For large-volume infusion solutions, such monitoring of water or intermediates should always be done. When a sample fails a test, the cause of failure should be investigated and remedial action taken.

20. Active pharmaceutical ingredients

In the manufacture of active pharmaceutical ingredients, the manufacturer should follow good manufacturing practices to ensure that the products are of the high quality.

20.1.1 Personnel responsible for the production and quality control of active pharmaceutical ingredients should have appropriate education, technical knowledge, and practical experience related to the job they perform.

20.1.2 There should be an adequate number of personnel and an organization chart. Individual responsibilities should be laid down in written instructions.

20.1.3 staff at all levels should be adequately trained for the tasks assigned to them.

20.1.4 Measures should be taken to ensure that no person affected by a disease in a communicable form or having open lesions on the exposed surface of the body is engaged in any production step involving direct contact with the active pharmaceutical ingredients.

20.2 Premises

20.2.1 Premises must be located, designed, constructed to suit the operations to be carried out. They should be of a suitable size for their intended use and should not contribute to actual or potential mix-ups or contamination of the active pharmaceutical ingredients

20.2.2 For special purposes, such as the production of sterile products and of certain antibiotics, hormones, and cytotoxic substances, separate specifically designed enclosed areas with completely separate air-handling systems should be provided.

20.2.3 The premises should include facilities for changing clothes, washing, and toilet purposes as well as for eating, drinking, and smoking.

20.3 Equipment

20.3.1 Equipment should be designed, constructed, located, and maintained in such a way as to
- be suitable for its intended use;
- facilitate thorough cleaning;
- minimize the risk of contamination of products;
- facilitate efficient operation.

20.3.2 Production and testing equipment should be cleaned, sterilized when necessary, used, and maintained in accordance with specific written instructions. Before production of another product is started, multi-purpose equipment used should be thoroughly cleaned and checked for cleanliness. Appropriate records of such procedures should be maintained.

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

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

20.4 Sanitation

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

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

20.4.3 Eating and smoking should not be permitted in manufacturing areas.

20.5 Documentation

20.5.1 Master formulae

20.5.1.1 There should be a master formula setting out in writing the raw materials and packaging materials (quality and quantity), as well as detailed production and quality control procedures for each active pharmaceutical ingredient and batch size. The master formula should be regularly reviewed and kept up to date.

20.5.1.2 Authorized persons 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. Copies of the master formula should be prepared in a manner that will eliminate any possibility of transcription error.

20.5.1.3 When the master formula need to be amended. Any amendments must be formally approved, signed and dated by authorized persons.

20.5.1.4 Outdated master formulae should be withdrawn but retained for reference.

20.5.2 Batch manufacturing record

20.5.2.1 There should be a batch manufacturing record of each batch to be manufactured. It should contain the relevant parts of the master formula and should include the following:

(1) the name of the product and the code reference where applicable;

(2) the batch number;

(3) the stages of production and the dates of the different stages;

(4) batch size;

(5) the batch number or analytical control number of raw materials used in the production;

(6) production details, including reference to the main equipment used;

(7) actual yield;

(8) a record of the in-process controls and the results obtained;

(9) details of, and signed authorization with the date for, any deviation from the master formula;

(10) any recovered materials, e.g. solvent, and procedures applied;

(11) the initials of the operators and signature of the person responsible for the production operations and the date of signature;

(12) all analytical records relating to the batch;

(13) a decision for the release or rejection of the batch;

(14) Production and control records should be reviewed and any divergence or failure of a batch to meet its specifications should be thoroughly investigated. A written record of the investigation should be made and should include the conclusion and follow-up action.

20.5.3 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. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs, or other means.

20.6 Retention of records and reference samples

20.6.1 Production and control records should be kept at least 5 years.

20.6.2 Reference samples of each batch of the active pharmaceutical ingredients should be retained at least one year beyond the expiry date or at least 5 years after manufacturing date if there is no expiry date.

20.7 Production

20.7.1 Processing

20.7.1.1 Processing should be carried out in accordance with the master formula. Steps that are critical for the quality of the active pharmaceutical ingredient should be defined and the processing procedures applied should be validated.

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

20.7.2 Raw materials

Raw 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.

20.7.3 Intermediate products

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

20.7.4 Active pharmaceutical ingredients

20.7.4.1 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.

20.7.4.2 For the production of sterile active pharmaceutical ingredients, section 19 ("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.

20.7.5 Packaging

20.7.5.1 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.

20.7.5.2 Good packaging procedures must be employed to prevent packaging errors and to ensure that the packaged products have quality as required and have the correct labels applied to the containers.

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

(1) the name of the product;
(2) its quality, if specified;
(3) the batch number;
(4) the expiry or retest date, if specified;
(5) warnings, if required;
(6) storage conditions, if specified;
(7) the names of the manufacturer and the supplier.

20.8 Quality control

20.8.1 There should be an independent quality control unit, the head of which is directly responsible to the management of the firm. The principal duties of the quality control unit are listed below.

20.8.1.1 It should approve:

- specifications and testing methods for raw materials, packaging materials, intermediate products and active pharmaceutical ingredients;
- sampling procedures;
- instructions regarding sanitation and hygiene;
- reprocessing procedures for rejected batches or recovered materials;
- other instructions related to the quality of the product.

20.8.1.2 It should be responsible for the release or rejection of raw materials, packaging materials, intermediate products, and active pharmaceutical ingredients.

20.8.1.3 It should ensure that the stability of active pharmaceutical ingredients is monitored.

20.8.1.4 It should be responsible for the investigation of complaints related to the quality of active pharmaceutical ingredients.

20.8.2 Every manufacturer should have 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 at suitable intervals and reagents should be of appropriate quality.

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

20.9 Stability studies

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

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

20.9.3 Expiry dates should be set for active pharmaceutical ingredients that are not stable. The products should be retested as necessary.

20.10 Self-inspection

The manufacturer should designate an expert or a team of experts to conduct regular independent inspections of its overall production and control procedures. Self-inspections should be recorded.

20.11 Storage

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

20.11.2 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.

20.12 Complaints and defects

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

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

20.12.3 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.

20.13 Rejected materials

The manufacturer should have written instructions concerning the handling of rejected materials, whether raw 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.