بسم الله الرحمن الرحيم

Maldives Food and Drug Authority

Ministry of Health

Male', Maldives

Guideline on Good Manufacturing Practices

Guideline on Good Manufacturing Practices is released under the authority of

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Male'
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Guideline on Good Manufacturing Practices

1 INTRODUCTION

The manufacturers of medicines are responsible for the development and manufacture of licensed medicines. Manufacturers shall adhere to Good Manufacturing Practices (GMP) to ensure the quality and safety of the medicines are consistent with the standards and specifications.

2 PURPOSE

This guideline outlines the GMP requirements set out by Maldives Food and Drug Authority (MFDA)/ Medicine and Therapeutic Goods Division (MTG) for medicines manufactured in or imported to the Maldives. This guideline is aimed at informing the stakeholders, medicines importers and manufacturers on the requirements for Good Manufacturing Practices (GMP) in the Maldives.

3 SCOPE

The GMP requirements specified in this guideline is applicable for the pharmaceuticals, alternative medicines, traditional and complementary medicines, herbal medicines, etc. that are licensed by the Maldives Food and Drug Authority (MFDA).

4 Guideline Content

4.1 What are the GMP requirements for imported products?

4.1.1 Medicines that are licensed to be imported to the Maldives require GMP certification from the national medicines regulatory authority of the country of manufacture. This is to ensure that the manufacturing processes and its facilities conform to the internationally accepted standards of GMP.

4.1.2 The GMP certificate of the manufacturer shall:

- comply with the WHO standard for GMP certificate
- have a validity of at least six months

4.1.3 MFDA as the national regulatory authority may visit the manufacturing sites for inspection and assure compliance to GMP and other quality and safety standards and specifications.

4.2 What are the GMP requirements for local products?

4.2.1 The locally manufactured shall meet minimum standards for GMP requirements set out by the WHO draft text for Good Manufacturing Practices (GMP) as these products are produced for the local market and not for exporting to international market.

4.3 Minimum standards for GMP

4.3.1 Sanitation and Hygiene

4.3.1.1 A high level of sanitation and hygiene should be practised in every aspect of the manufacture of medicines. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene

4.4 Qualification and validation

4.4.1 Complaints

4.4.1.1 All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken.

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

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

4.4.1.4 Special attention should be given to establishing that the product that gave rise to a complaint was defective.

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

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

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

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

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

4.4.1.10 MFDA should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, a suspect product or any other serious quality problems with a product.

4.5 Product recalls[1]

[1] Refer to MFDA/MTG's "Guideline for reporting Quality Defects and Product Recall" for further information

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

4.5.2 The authorized person should be responsible for the execution and coordination of recalls. He or she should have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.

4.5.3 There should be established written procedures, which are regularly reviewed and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly down to the required level in the distribution chain.

4.5.4 An instruction should be included in the written procedures to store recalled products in a secure segregated area while their fate is decided.

4.5.5 MFDA/MTG should be promptly informed of any intention to recall the product because it is, or is suspected of being, defective.

4.5.6 The distribution records should be readily available to the authorized person, and they should contain sufficient information on wholesalers and directly supplied customers to permit an effective recall.

4.5.7 The progress of the recall process should be monitored and recorded. Records should include the disposition of the product. A final report should be issued, including a reconciliation between the delivered and recovered quantities of the products.

4.5.8 The effectiveness of the arrangements for recalls should be tested and evaluated from time to time.

4.6 Contract Production, analysis, and other activities

4.6.1.1 Self-inspection, quality audits and suppliers' audits and approval

4.6.1.2 *Principle*. The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and Quality Control. The self- inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

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

a. personnel;
b. premises including personnel facilities;
c. maintenance of buildings and equipment;
d. storage of starting materials and finished products;
e. equipment;
f. production and in-process controls;
g. Quality Control;
h. documentation;
i. sanitation and hygiene;
j. validation and revalidation programmes;
k. calibration of instruments or measurement systems;
l. recall procedures;
m. complaints management;
n. labels control;
o. results of previous self-inspections and any corrective steps taken

4.6.1.4 **Self-inspection team:** Management should appoint a self-inspection team consisting of experts in their respective fields who are familiar with GMP. The members of the team may be appointed from inside or outside the company**.**

4.6.1.5 **Frequency of self-inspection:** The frequency with which self-inspections are conducted may depend on company requirements but should preferably be at least once a year. The frequency should be stated in the procedure

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

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

4.6.1.7 **Follow-up action:** There should be an effective follow-up programme. The company management should evaluate both the self-inspection report and the corrective actions as necessary

4.6.1.8 **Quality Audit:** It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (see section 7, "Contract production and analysis").

4.7 Suppliers' audits and approval

4.7.1 The person responsible for Quality Control should have responsibility, together with other relevant departments, for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

4.7.2 Before suppliers are approved and included in the approved suppliers' list or specifications, they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier's ability to conform with GMP standards.

4.8 Personnel

4.8.1 **Principle**: The establishment and maintenance of a satisfactory system of QA and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason, there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

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

4.8.3 Responsible staff should have specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Duties may be delegated to designated deputies with a satisfactory level of qualifications. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP. The manufacturer should have an organization chart.

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

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

4.8.6 **Key personnel:** Key personnel include the heads of production, the head(s) of quality unit(s) and the authorized person. The quality unit(s) typically comprise the quality assurance and quality control functions. In some cases, these could be combined in one department. The authorized person may also be responsible for one or more of these quality unit(s). Normally, key posts should be occupied by full-time personnel. The heads of production and quality unit(s) should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated[2].

4.8.7 Key personnel responsible for supervising the production and quality unit(s) for medicinal products should possess the qualifications and practical experience required by national legislations and by-laws. In order to gain such experience, a preparatory period may be required, during which they should perform their duties under professional guidance. The education and practical experience of experts should be such as to enable them to exercise independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and Quality Control of medicinal products.

4.9 Training

[2] For further guidance on responsibilities of key personnel, refer to the WHO draft text guideline for GMP

4.9.1 The manufacturer should provide training in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel as required.

4.9.2 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 periodically assessed. Approved training programmes should be available. Training records should be kept.

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

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

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

4.9.6 Consultant and contract staff should be qualified for the services they provide. Evidence of this should be included in the training records

4.10 Personal Hygiene

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

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

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

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

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

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

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

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

4.11 Premises

4.11.1 **Principle:** Premises must be located, designed, constructed, adapted and maintained to suit the operations to be carried out.

4.11.2 General:

4.11.2.1 The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross- contamination, build-up of dust or dirt, and in general, any adverse effect on the quality of products.

4.11.2.2 Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, or packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning.

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

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

4.11.2.5 Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products.

4.11.2.6 Premises should be cleaned and, where applicable, disinfected according to detailed written procedures. Records should be maintained.

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

4.11.2.8 Premises should be designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals. There should be a procedure for rodent and pest control.

4.11.2.9 Premises should be designed to ensure the logical flow of materials and personnel.

4.11.3 Ancillary areas:

4.11.3.1 Rest and refreshment rooms should be separate from manufacturing and control areas.

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

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

4.11.4 Storage areas:

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

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

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

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

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

4.11.4.6 Highly active and radioactive materials, narcotics, other dangerous medicines, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.

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

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

4.11.5 Weighing areas:

4.11.5.1 The weighing of starting materials and the estimation of yield by weighing should be carried out in separate weighing areas designed for that use, for example, with provisions for dust control. Such areas may be part of either storage or production areas.

4.11.6 Production areas:

4.11.6.1 To minimize the risk of a serious medical hazard due to cross- contamination, dedicated and self-contained facilities must be available for the production of particular products. The production of certain other highly active products should not be conducted in the same facilities.

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

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

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

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

4.11.6.6 Drains should be of adequate size and designed 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.

4.11.6.7 Production areas should be effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination.

4.11.7 Equipment

4.11.7.1 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 minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

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

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

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

4.11.7.5 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated according to a fixed schedule.

4.11.7.6 Production equipment should be thoroughly cleaned according to a fixed schedule.

4.11.7.7 Laboratory equipment and instruments should be suited to the testing procedures undertaken.

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

4.11.7.9 Production equipment should not present any hazard to the products. The parts of the production equipment that come to contact with the product must not be reactive, additive, or absorptive to an extent that would affect the quality of the product.

4.11.7.10 Defective equipment should be removed from production and Quality Control areas. If this is not possible, it should be clearly labelled as defective to prevent use.

4.11.7.11 Closed equipment should be used whenever appropriate. Where open equipment is used or equipment is opened, precautions should be taken to minimize contamination.

4.11.7.12 Non-dedicated equipment should be cleaned according to validated cleaning procedures between being used for production of different pharmaceutical products to prevent cross-contamination.

4.11.7.13 Current drawings of critical equipment and support systems should be maintained.

4.11.8 Materials

4.11.8.1 **Principle**: The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (starting and packaging).

4.11.8.2 Materials include starting materials, packaging materials, gases, solvents, process aids, reagents, and labelling materials.

4.11.8.3 No materials used for operations such as cleaning, lubrication of equipment and pest control should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g. food grade) to minimize health risks.

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

4.11.8.5 All materials and products should be stored under the appropriate conditions established by the manufacturer, and in an orderly fashion, to permit batch segregation and stock rotation by a first-expire, first-out rule.

4.11.8.6 Water used in the manufacture of pharmaceutical products should be suitable for its intended use.

4.11.9 Starting materials:

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

4.11.9.2 Starting materials should be purchased only from approved suppliers and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is beneficial for all critical aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements as well as complaints and rejection procedures, to be contractually agreed between the manufacturer and the supplier.

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

4.11.9.4 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled, if required, with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.

4.11.9.5 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.

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

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

a. the designated name of the product and the internal code reference where applicable;
b. the batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;
c. (the status of the contents (e.g. in quarantine, on test, released, rejected, returned, recalled);
d. where appropriate, an expiry date or a date beyond which retesting is necessary. When fully validated computerized storage systems are used, not all of the above information need be in a legible form on the label.

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

4.11.9.9 Only starting materials released by the Quality Control department and within their shelf-life should be used.

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

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

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

4.11.10 Packaging materials:

4.11.10.1 The purchase, handling and control of primary and printed packaging materials should be as for starting materials.

4.11.10.2 Particular attention should be paid to printed packaging materials. They should be stored in secure conditions so as to exclude the possibility of unauthorized access. Roll feed labels should be used wherever possible. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix ups. Packaging materials should be issued for use only by designated personnel following an approved and documented procedure.

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

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

4.11.10.5 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions

4.11.11 Intermediate and bulk products:

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

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

4.11.12 Finished products:

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

4.11.13 Rejected, recovered, reprocessed, and reworked materials:

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

4.11.13.2 The reworking or recovery of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record should be kept of the reworking or recovery. A reworked batch should be given a new batch number.

4.11.13.3 The introduction of all or part of earlier batches, conforming to the required quality standards, into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life. The recovery should be recorded.

4.11.13.4 The need for additional testing of any finished product that has been reprocessed, reworked or into which a recovered product has been incorporated, should be considered by the QC department.

4.11.14 Recalled products:

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

4.11.15 Returned goods:

4.11.15.1 Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabelling, or alternative action taken only after they have been critically assessed by the QC function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.

4.11.15.2 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 re- standardization is due, and the storage conditions. The label should be signed and dated by the person preparing the reagent.

4.11.16 Reference standards:

4.11.16.1 Whenever official reference standards exist, these should preferably be used.

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

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

4.11.16.4 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization.

4.11.16.5 Reference standards should be properly labelled with at least the following information:

a. name of the material
b. batch or lot number and control number
c. date of preparation
d. shelf-life
e. potency
f. storage conditions

4.11.16.6 All in-house reference standards should be standardized against an official reference standard, when available, initially and at regular intervals thereafter.

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

4.11.17 Waste materials:

4.11.17.1 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

4.11.17.2 Waste material should not be allowed to accumulate. It 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 and frequent intervals.

4.11.18 Miscellaneous

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

4.12 Documentation

4.12.1 Principle: Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures 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 medicine for sale; to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases, some or all of the documents described below may be brought together, but they will usually be separate.

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

4.12.3 Documents should be approved, signed and dated by the appropriate responsible persons. No document should be changed without authorization and approval.

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

4.12.5 Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specific period of time.

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

4.12.7 Any alteration made to a document should be signed and dated; the alteration should be done in such a way as to permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

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

4.12.9 Data (and records for storage) may be recorded by electronic data- processing systems or by photographic or other reliable means. Master formulae and detailed SOPs 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 system, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked. Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, electronic discs, paper printouts or other means. It is particularly important that, during the period of retention, the data are readily available.

4.12.10 Documents required:

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

4.12.10.2 All finished medicines should be identified by labelling, as required by the national legislation, bearing at least the following information:

a. the name of the medicines;

b. a list of the active ingredients (if applicable, with the INN), showing the amount of each present and a statement of the net contents (e.g. number of dosage units, weight, volume);

c. the batch number assigned by the manufacturer;

d. the expiry date in an uncoded form;

e. any special storage conditions or handling precautions that may be necessary;

f. directions for use, and warnings and precautions that may be necessary;

g. the name and address of the manufacturer or the company or the person responsible for placing the product on the market.

4.12.10.3 For reference standards, the label and/or accompanying document should indicate potency or concentration, date of manufacture, expiry date, date the closure is first opened, storage conditions and control number, as appropriate.

4.12.11 Specifications and testing procedures:

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

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

4.12.11.3 Each specification should be approved, signed and dated, and maintained by the QC or QA units.

4.12.11.4 Periodic revisions of the specifications may be necessary to comply with new editions of the official compendia.

4.12.12 Specifications for starting and packaging materials:

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

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

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

a. the supplier and the original producer of the materials;
b. a specimen of printed materials;

c. directions for sampling and testing, or a reference to procedures;
d. storage conditions and precautions;
e. the maximum period of storage before re-examination.

4.12.12.2 Packaging material should conform to specifications, and should be compatible with the material and/or with the medicines it contains. The material should be examined for compliance with the specification, and for defects as well as for the correctness of identity markings.

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

4.12.13 Specifications for intermediate and bulk products

4.12.13.1 Specifications for intermediate and bulk products should be available. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

4.12.14 Specifications for finished products

4.12.14.1 Specifications for finished products should include:

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

4.12.15 Master formulae

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

4.12.15.2 The master formula should include (where applicable):

a. the name of the product, with a product reference code relating to its specification;
b. a description of the dosage form, strength of the product and batch size;

c. a list of all starting materials to be used, with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);
d. a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
e. a statement of the processing location and the principal equipment to be used;
f. the methods, or reference to the methods, to be used for preparing and operating the critical equipment, e.g. cleaning (especially after a change in product), assembling, calibrating, sterilizing, use;
g. detailed step-wise processing instructions (e.g. checks on materials, pre-treatments, sequence for adding materials, mixing times, temperatures);
h. the instructions for any in-process controls with their limits;
i. where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions;
j. any special precautions to be observed.

4.12.16 Packaging instructions

4.12.16.1 Formally authorized packaging instructions should exist for each product, pack size and type.

These should normally include, or make reference to:

a. the name of the product;
b. a description of its pharmaceutical form, strength and, where applicable, method of application;
c. the pack size expressed in terms of the number, weight or volume of the product in the final container;
d. a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications for each packaging material;
e. where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;
f. special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations;
g. a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
h. details of in-process controls with instructions for sampling and acceptance limits.

4.12.17 Batch processing records

4.12.17.1 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programs are recommended. Transcribing from approved documents should be avoided.)

4.12.17.2 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.

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

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

4.12.18 Batch packaging records:

4.12.18.1 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the approved packaging instructions, and the method of preparing such records should be designed to avoid errors. (Copying or validated computer programs are recommended. Transcribing from approved documents should be avoided.)

4.12.18.2 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.

4.12.18.3 The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:

a. the name of the product, the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;
b. the date(s) and time(s) of the packaging operations;
c. the name of the responsible person carrying out the packaging operation;
d. the initials of the operators of the different significant steps;
e. the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
f. details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product if it is unpacked or a record of returning product that has not been packaged to the storage area;
g. whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;
h. notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
i. the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

4.12.19 Standard operating procedures and records:

4.12.19.1 SOPs and associated records of actions taken or, where appropriate, conclusions reached should be available for:

a. equipment assembly and validation;
b. analytical apparatus and calibration;
c. maintenance, cleaning and sanitization;
d. personnel matters including qualification, training, clothing and hygiene;
e. environmental monitoring;
f. pest control;
g. complaints;
h. recalls;

i. returns.

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

4.12.19.3 The records of the receipts should include:

a. the name of the material on the delivery note and the containers;
b. the "in-house" name and/or code of material if different from (a);
c. the date of receipt;
d. the supplier's name and, if possible, manufacturer's name;
e. the manufacturer's batch or reference number;
f. the total quantity, and number of containers received;
g. the batch number assigned after receipt;
h. any relevant comment (e.g. state of the containers).

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

4.12.19.5 SOPs should be available for each instrument and piece of equipment (e.g. use, calibration, cleaning, maintenance) and placed in close proximity to the equipment.

4.12.19.6 There should be SOPs for sampling, which specify the person(s) authorized to take samples.

4.12.19.7 The sampling instructions should include:

a. the method of sampling and the sampling plan;
b. the equipment to be used;
c. any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
d. the amount(s) of sample(s) to be taken;
e. instructions for any required subdivision of the sample;
f. the type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling, and labelling;
g. any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

4.12.19.8 There should be an SOP describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.

4.12.19.9 The SOPs for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.

4.12.19.10 The SOP for batch numbering should ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.

4.12.19.11 Batch-number allocation should be immediately recorded, e.g. in a logbook. The record should include at least the date of allocation, product identity and size of batch.

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

4.12.19.13 Analysis records should include at least the following data:

a. the name of the material or product and, where applicable, dosage form;
b. the batch number and, where appropriate, the manufacturer and/ or supplier;
c. references to the relevant specifications and testing procedures;
d. test results, including observations and calculations, and reference to any specifications (limits);
e. date(s) and reference number(s) of testing;
f. the initials of the persons who performed the testing;
g. the date and initials of the persons who verified the testing and the calculations, where appropriate;
h. a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

4.12.19.14 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.

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

4.12.19.16 Records should be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning or repair operations, including dates and the identity of the people who carried out these operations.

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

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

4.13 Good practices in production

4.13.1 Principle: Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

4.13.2 General

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

4.13.2.2 Deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be in accordance with an approved procedure. The authorization of the deviation should be approved in writing by a designated person, with the involvement of the QC department, when appropriate.

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

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

4.13.2.5 At all times during processing, all materials, bulk containers, major items of equipment, and, where appropriate, the rooms and packaging lines being 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. In some cases, it may be useful to also record the name of the previous product that has been processed.

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

4.13.2.7 Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.

4.13.2.8 In-process controls are usually performed within the production area. The performance of such in-process controls should not have any negative effect on the quality of the product or another product (e.g. cross-contamination or mix up).

4.13.3 Prevention of cross-contamination and bacterial contamination during production

4.13.3.1 When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g. supply and extraction of air of suitable quality).

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

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

a. carrying out production in dedicated and self-contained areas (which may be required for products such as penicillin, live vaccines, live bacterial preparations and certain other biologicals);
b. conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;
c. providing appropriately designed airlocks, pressure differentials, and air supply and extraction systems;
d. minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
e. wearing protective clothing where products or materials are handled;
f. using cleaning and decontamination procedures of known effectiveness;
g. using a "closed system" in production;
h. testing for residues;
i. using cleanliness status labels on equipment.

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

4.13.3.5 Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g. for microbiological and particulate matter, where appropriate).

4.13.4 Processing operations

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

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

4.13.4.3 Means should be instituted of indicating failures of equipment or of services (e.g. water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. After use, production equipment should be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.

4.13.4.4 Time limits for storage of equipment after cleaning and before use should be stated and based on relevant data.

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

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

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

4.13.4.8 Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes should be sanitized and stored according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

4.13.4.9 Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at pre-specified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated on a label attached to the instrument.

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

4.13.5 Packaging operations

4.13.5.1 When the programme for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix ups or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or an alternative system that will provide equal assurance.

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

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

4.13.5.4 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.

4.13.5.5 The correct performance of any printing (e.g. of code numbers or expiry dates) done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand, which should be rechecked at regular intervals.

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

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

4.13.5.8 Regular online control of the product during packaging should include at a minimum check on:

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

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

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

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

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

4.13.5.13 Production records should be reviewed as part of the approval process of batch release before transfer to the authorized person. Any divergence or failure of a batch to meet production 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.

4.14 Good practices in quality control

4.14.1 QC is the part of GMP concerned with sampling, specifications and testing, and with the organization and documentation 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 compliant with the requirements. QC is not confined to laboratory operations, but may be involved in many decisions concerning the quality of the product.

4.14.2 The independence of QC from production is considered fundamental.

4.14.3 Each manufacturer should have a QC function. The QC function should be independent of other departments and under the authority of a person with appropriate qualifications and experience. Adequate resources must be available to ensure that all the QC arrangements are effectively and reliably carried out. The basic requirements for QC are as follows:

a. adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
b. samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved by the QC department;
c. qualification and validation;
d. records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated;
e. the finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container and correctly labelled;

f. records must be made of the results of inspecting and testing the materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;
g. sufficient samples of starting materials and products must be retained to permit future examination of the product if necessary; the retained product must be kept for the appropriate time in its final pack unless the pack is exceptionally large, in which case one that is equivalent to the marketed packaging system may be used.

4.14.4 Other QC responsibilities include:

a. establishing, validating and implementing all QC procedures;
b. evaluating, maintaining and storing reference standards for substances;
c. ensuring the correct labelling of containers of materials and products;
d. ensuring that the stability of the active pharmaceutical ingredients and products is monitored;
e. participating in the investigation of complaints related to the quality of the product;
f. participating in environmental monitoring;
g. participation in QRM programmes.

4.14.5 Control of starting materials and intermediate, bulk and finished products

4.14.5.1 These activities should be carried out in accordance with written procedures and, where necessary, recorded.

4.14.5.2 QC personnel must have access to production areas for sampling and investigation as appropriate.

4.14.5.3 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.

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

4.14.5.5 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.

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

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

4.14.5.8 Each sample container should bear a label indicating:

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

4.14.5.9 Out-of-specification results obtained during testing of materials or products should be investigated in accordance with an approved procedure. Records should be maintained.

4.14.6 Test requirements: Starting and packaging materials

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

4.14.6.2 An identity test should be conducted on a sample from each container of starting material (see also section 14.14). It is permissible to sample only a proportion of the containers where a validated procedure has been established to ensure that no single container of starting material has been incorrectly labelled. This validation should take account of at least the following aspects:

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

4.14.6.3 Under such a system it is possible that a validated procedure for exemption from the requirement for identity testing of each incoming container of starting material could be accepted for the following:

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

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

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

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

4.14.6.5 In lieu of full testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results (see sections 8.8 and 8.9) and through on-site audits of the supplier's capabilities. (This does not affect section 17.15.) Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain at least the following information (7):

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

4.14.7 In-process control

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

4.14.8 Finished products

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

4.14.8.2 Products failing to meet the established specifications or any other relevant quality criteria should be rejected.

4.14.9 Batch record review

4.14.9.1 QC records should be reviewed as part of the approval process of batch release before transfer to the authorized person. 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.

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

4.14.10 Stability studies

4.14.10.1 QC should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.

4.14.10.2 QC should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

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

a. a complete description of the medicine involved in the study;
b. the complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
c. provision for the inclusion of a sufficient number of batches;
d. the testing schedule for each medicine;

e. provision for special storage conditions;
(f) provision for adequate sample retention;
f. a summary of all the data generated, including the evaluation and the conclusions of the study.

4.14.10.4 Stability should be determined prior to marketing and following any significant changes, for example, in processes, equipment or packaging materials.

5 Reference documents:

- Medicine Regulation 2014/R-46
- WHO draft text on Good Manufacturing Practices (GMP)/ WHO good manufacturing practices for pharmaceutical products: main principles