PHARMACY, MEDICINES AND POISONS BOARD GOOD MANUFACTURING PRACTICES GUIDELINES(GMP)

Table of Contents

20.1.7 Personnel

20.1.8 Sanitation

20.1.9 Manufacturing control

20.2.0 Sterilization by heat

20.2.1 Sterilization by moist heat

20.2.2 Sterilization by dry heat

20.2.3. Sterilization by radiation

20.2.4 Sterilization by ethylene oxide

20.2.5 Aseptic filling operations

20.2.6 Sterilization by filtration

20.2.7 Blow/Fill/Seal

20.2.8 Isolator technology

20.2.9 Quality control

PART ONE: NON-STERILE PRODUCTS

1.0 INTRODUCTION

The Pharmacy, Medicines and Poisons Board (PMPB) has the mandate to ensure that medicines supplied to the public are safe, efficacious and of good quality. The Board partly does this through inspections that are meant to enforce compliance with current good manufacturing practices (cGMP) by pharmaceutical manufacturers.

GMP is that part of quality assurance which ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their use. It ensures that quality is built into the organization and manufacturing processes. It covers all manufacturing aspects that include transportation, receipt of raw materials, storage, quality control, and delivery of the product.

Objective

To provide guidance to experts when undertaking cGMP inspections of manufacturing plants

Scope

The guidelines apply to human medicines and veterinary medicines.

2.0 Current Good Manufacturing Practices (cGMP) for Medicines

cGMP is the part of quality assurance that ensures that medicines are consistently produced and controlled in such a way to meet the quality standards appropriate to their intended use, as required by the **Regulatory Authority**.

2.1 Basic **principles to be verified during GMP inspections**:

(a) Manufacturing processes are clearly defined and controlled to ensure consistency and compliance with approved specifications.

(b) Critical steps of manufacturing processes and significant changes to the process are validated.

(c) All necessary key elements for GMP are provided, including the following:

- qualified and trained personnel,

- adequate premises and space,
- suitable equipment and services,
- correct materials, containers and labels,
- approved procedures and instructions,
- suitable storage and transport.

(d) Instructions and procedures are written in clear and unambiguous language;

(e) Operators are trained to carry out and document procedures;

(f) Records are made during manufacture that demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the drug was as expected. Deviations are investigated and documented.

(g) Records of manufacture, packaging, labeling, testing, distribution, importation, and wholesaling that enable the complete history of a lot to be traced are retained in a comprehensible and accessible form;

(h) Control of storage, handling, and transportation of the drugs minimizes any risk to their quality;

(i) A system is available for recalling of drugs from sale;

(j) Complaints about **Medicines** are examined, the causes of quality defects are investigated, and appropriate measures are taken with respect to the defective **medicines** and to prevent recurrence.

2.2 BASIC REQUIREMENTS FOR CGMP INSPECTIONS

2.2.1 Quality Control

Quality control is the part of cGMP that is concerned with sampling, specifications, testing, documentation, and release procedures. Quality control ensures that the necessary and relevant tests are carried out and that raw materials, packaging materials, and products are released for use or sale, only if their quality is satisfactory.

2.2.2 Quality control requirements are as follows:

(a) Adequate facilities, trained personnel, and approved procedures are available for sampling, inspecting and testing of raw materials, packaging materials, intermediate bulk and finished products, and, where appropriate monitoring environmental conditions for GMP purposes.

(b) Samples of raw materials, packaging materials, and intermediate, bulk, and finished products are taken according to procedures approved by the quality control department.

(c) Test methods are validated.

(d) Records demonstrate that all the required sampling, inspecting, and testing procedures are carried out, and any deviations are recorded and investigated.

(e) Records are made of the results of the inspection and testing of materials and finished products against specifications.

(f) The procedures for product release include a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures.

(g)No drug is released for sale or supply prior to approval by the quality control department.

(h) Sufficient samples of raw material and finished product are retained to permit future examination if necessary.

2.2.3 Quality assurance

Quality assurance is a wide-ranging concept that covers all matters that individually or collectively influence the quality of a medicine. It is the total of the organized arrangements made with the objective of ensuring that medicines are of the quality required for their intended use. Quality assurance therefore incorporates cGMP, along with other factors that are outside the scope of these guidelines.

A system of quality assurance appropriate for the manufacture, packaging, labeling, testing, distribution, importation, and wholesale of medicines should ensure that:

(a) Medicines are designed and developed in a way that takes into account the cGMP requirements;

(b) Managerial responsibilities are clearly specified;

(c)Systems, facilities and procedures are adequate and qualified;

(d) Production and control operations are clearly specified;

(e) Analytical methods and critical processes are validated;

(f) Arrangements are made for the supply and use of the correct raw and packaging materials;

(g)All necessary **controls** on intermediates, and any other in-process monitoring **are** carried out;

(h) Outsourced activities are subject to appropriate controls and meet cGMP requirements;

(i) Manufacture, packaging/labeling, testing, distribution, importation, and wholesaling are performed in accordance with established procedures;

(j) Medicines are not sold or supplied before the quality control department has certified that each lot has been produced and controlled in accordance with the marketing authorization and of any other regulations relevant to the production, control and release of **medicines**;

(k) Satisfactory arrangements exist for ensuring that the medicines are stored, distributed, and subsequently handled in such a way that quality is maintained throughout their shelf life;

(l) The quality risk management system should ensure that:

- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient
- the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

(m)The effectiveness, applicability, and continuous improvement of the quality management system is **assured** through regular management review and self-inspection;

(n)An annual product quality review of all **medicines** should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both raw materials and finished product to highlight any trends and to identify product and process improvements.

2.2.3 QUALITY MANAGEMENT

The quality objective is to ensure that the manufacture, packaging, labeling, distribution, testing and wholesaling of medicines comply with stipulated regulations and do not place consumers at risk due to inadequate safety and quality.

The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of personnel in many different departments and at all levels within the establishment and its suppliers. To ensure compliance, there must be a comprehensively designed and correctly implemented quality management system that incorporates cGMP and quality control. The system should be fully documented and its effectiveness monitored. All parts of the quality management system should be adequately resourced with qualified personnel, suitable premises, equipment, and facilities.

2.2.4 DOCUMENTATION

Good documentation is key to complying with cGMP requirements. The various types of documents and media used should be fully defined. Documentation may exist in various forms

including paper based, electronic or photographic media. The main objective of the system of documentation utilized must be to establish,control,monitor and record all activities which directly or indirectly impact on all aspects of the quality of medicinal products. Primary types of documentation used to manage and record cGMP compliance are instructions (directions, requirements) and records/reports. Appropriate good documentation practice should be applied with respect to the type of document. Suitable controls should be implemented to ensure the accuracy, integrity and availability and legibility of documents. Instruction documents should be free from errors and available in writing.

Documentation requirements are as follows:

(a) Site master file: A document describing the GMP related activities of the manufacturer

(b) Instructions (directions or requirements) type:

- **Specifications**: It describes in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as basis for quality evaluation.
- **Master formulae, processing, packaging and testing instructions**: These provide details of all starting materials, equipment and computerised systems (if any) to be used and specify all processing and packaging, sampling and testing instructions, in-process controls and process analytical technologies together with acceptance criteria.
- Standard Operating Procedures (SOP) These give direction for performing certain operations.
- **Protocols:** These give instructions for performing and recording certain discreet operations.
- **Technical agreements**: These are agreements made between contract giver and acceptor for outsourced activities.

(c)Record/Report type:

- **Records**: These provide evidence of various actions taken to demonstrate compliance with instructions e.g. activities, events, investigations and in the case of manufactured batches a history of each batch of product, including its distribution. Records include the raw data which is used to generate other records. For electronic records, regulated users should define which data are to be used as raw data. At least all data on which quality decisions are based should be defined as raw data. Certificate of analysis (COA). Provide a summary of testing results on samples of products or materials together with the evaluation for compliance to a stated specification.
- **Reports:** These document the conduct of particular exercises, projects or investigations together with results, conclusions and recommendations.

RECORDS

The following documents are maintained by the manufacturer, packager/labeler, distributor, wholesaler, and importer of a medicine as they relate to all operations:

- Distribution records of all sales of drugs, including those of professional samples.
- Records of all sales are retained or are kept readily accessible in a manner that will permit a complete and rapid recall of any lot or batch of a drug. This requirement need not necessarily involve tracking by lot number.
- Records to indicate that all customers who have received a recalled drug have been notified.
- Records of the results of the self-inspection program, evaluation, and conclusions, and corrective measures implemented.

The following documents are maintained by every manufacturer, packager/labeler, distributor, wholesaler, and importer of a drug:

- Records of complaints or any information respecting the quality of a medicine or its deficiencies or hazards, and of subsequent investigations of complaints, including corrective actions taken.
- Records concerning information received respecting the quality of a medicine or its deficiencies or hazards.

The following documents are maintained by the manufacturer:

- the written specifications for the raw materials;
- the results of the raw material testing;
- the sources of the raw materials supplied;
- records on the operation of the sanitation program required by PMPB Regulations and
- Detailed plans and specifications of each building where fabrication occurs, including a description of the design and construction.

The following documents are maintained by the person who packages or labels a drug:

- the written specifications for the packaging materials;
- the results of the packaging material examinations or testing;
- the sources of the packaging materials supplied; and
- records on the operation of the sanitation program

Every manufacturer, packager/labeler, and tester maintains:

- Details of the personnel employed to supervise the manufacture, packaging/labeling, and testing, including organization charts; each person's title, job description, responsibilities, qualifications, experience, and training; and the name(s) of each person's designated alternate(s).

Records required are retained for a period of at least one year past the expiration date of the drug to which the records apply.

GENERATION AND CONTROL OF DOCUMENTATION

(i) All types of documents should be defined and adhered to. The requirements apply to all forms of document media types. Complex systems need to be understood, well documented, validated and adequate controls should be in place. Many documents (instructions and /or records may exist in hybrid forms i.e .some elements are electronic and others are paper based. Relationships and control measures for master documents, official copies, data handling and records need to be stated for both hybrid and homogeneous systems. Appropriate controls for electronic documents such as templates, forms and master and other documents should be implemented. Appropriate controls should be in place to ensure the integrity of the record throughout the retention period.

(ii) Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of product specification files, manufacturing and marketing authorization dossiers as appropriate. The reproduction of working documents from master documents should not allow any error to be introduced through the reproduction process.

(iii)Documents containing instructions should be approved, signed and dated by appropriate and authorized persons. Documents should have unambiguous contents and be uniquely identifiable. The effective date should be defined.

(iv) Documents containing instructions should be laid out in an orderly fashion and be easy to check. The style and language of documents should fit with their intended use. Standard operating procedures, work instructions and methods should be written in an imperative mandatory style.

(v) Documents within the quality management system should be regularly reviewed and kept up to date.

(vi) Documents should not be hand written, although where documents require the entry of data, sufficient space should be provided for such entries

GOOD DOCUMENTATION PRACTICES

(i) Hand written entries should be made in a clear, legible, indelible way.

(ii) Records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable.

(iii) Any alteration made to the entry on a document should be signed and dated; the alterations should permit reading of the original information. Where appropriate the reasons for alteration should be recorded.

RETENTION OF DOCUMENTS

(i) It should be clearly defined which record is related to each manufacturing activity and where this record is located. Some controls must be in place to ensure the integrity of the record throughout the retention period and validated where appropriate

(ii) Specific requirements apply to batch documentation which must be kept for 1 year after expiry of the batch to which it relates or at least 5 years after certification of the batch by qualified person, whichever is the longer. For investigational medicinal products, the batch documentation must be kept for at least 5 years after the completion or formal discontinuation of the last clinical trial in which the batch was used.

(iii) For other types of documentation, the retention period will depend on the business activity which the documentation supports. Critical documentation, including raw data (for example relating to validation or stability) which supports information in the marketing authorization should be retained whilst the authorization remain in force. It may be considered acceptable to retire certain documentation (eg raw data supporting validation reports or stability reports) where the data has been superseded by a full set of new data. Justification for this should be documented and should take into account the requirements for retention of batch documentation; for example in the case of process validation data, the accompanying raw data should be retained for a period at least as long as the records for all batches whose release has been supported on the basis of that validation exercise.

DOCUMENTATION SPECIFICATIONS

There should be appropriately authorized and dated specifications for starting and packaging materials and finished products.

(i) Specifications for starting and packaging materials

Specification for starting and primary or printed packaging materials should include or provide reference to, if applicable:

(a) A description of the materials including:

-the designated name and the internal code reference

-the reference if any, to a pharmacopoeal monograph

-the approved suppliers and if reasonable, the original producer of the material

-A specimen of printed material

(b) Directions for sampling and testing

(c)Qualitative and quantitative requirements with acceptance limits

(d) Storage conditions and precautions

(e) The maximum period of storage before re-examination

(ii) Specifications for intermediate and bulk products

Specifications for intermediate and bulk products should be available for critical steps or if these are purchased or dispatched. The specifications should be similar to specifications for starting materials or for finished products as appropriate.

(iii) Specifications for finished products

These should include or provide reference to:

(a) The designated name of the product and the code reference where applicable
(b) The formula
(c) A description of the pharmaceutical form and package details
(d) Direction for sampling and testing
(e) The qualitative and quantitative requirements with acceptance limits
(f) The storage conditions and any special handling precautions, where applicable
(g) The shelf-life

(iv) Manufacturing formula and processing instructions

Approved, written manufacturing formula and processing instructions should exist for each product and batch size to be manufactured.

The manufacturing formula should include:

(a) The name of the product with a product reference code relating to its specification.
(b) A description of the pharmaceutical form, strength of the product and batch size.
(c) A list of all starting materials to be used with the amount of each, described; 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 acceptance limits and of relevant intermediate yields, where applicable.

(v) The processing instructions should include:

(a) A statement of the processing location and the principal equipment used.
(b) The methods or reference to the methods to be used for preparing the critical equipment (eg cleaning, assembling, calibrating, sterilizing).

(c) Checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process and that equipment is clean and suitable for use.
(d) Detailed stepwise processing instructions (eg checks on materials, pre-treatment sequence for adding materials, critical process parameters (time, temperature etc).
(e) The instructions for any in-process controls with their limits.
(f) Where necessary the requirements for bulk storage of the products, including the container, labeling and special storage conditions where applicable.
(g) Any special precautions to be observed.

(vi) Packaging instructions:

Approved packaging instructions for each product, pack size and type should exist. These should include and have reference to the following:

(a) Name of product including the batch number of bulk and finished product.

(b) Description of its pharmaceutical form and strength where applicable.

(c) The pack size expressed in terms of the number, weight or volume of the product in the final container.

(d) A complete list of all the packaging materials required including quantities, sizes and types with the code or reference number relating to the specifications of each packaging material.

(e) Where appropriate an example or reproduction of the relevant printed packaging materials and specimens indicating where to apply batch number references and shelf life of the product.

(f) Checks that the equipment and work station are clear of previous product, documents or materials not required for the planned packaging operations (line clearance) and that equipment is clean and suitable for use.

(g) Special precautions to be observed including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin.

(h) A description of the packaging operations including any significant subsidiary operations and equipment to be used.

(i) Details of in-process controls with instructions for sampling and acceptance limits.

(vii) Batch Processing Record

A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing formula and processing instructions and should contain the following information:

(a) The name and batch of the product
(b) Dates and times of commencement, of significant intermediate stages and of completion of production
(c) Identification(initials of the operator(s) who performed each significant step of the process and where appropriate the name of any person who checked these operations
(d) The batch number and/or analytical control number as well as the quantities of each starting material actually weighed(including the batch number and amount of any recovered or reprocessed material added)
(e) Any relevant processing operation or event and major equipment used
(f) A record of the in-process controls and initials of the persons carrying them out and the results obtained
(g) The product yield obtained at different and pertinent stages of manufacture
(h) Notes on special problems including details with signed authorization for any deviation from the manufacturing formula and processing instructions
(i) Approval by the person responsible for the processing operations

(viii) Batch Packaging Record

A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the packaging instructions.

The packaging record should contain the following information:

(a) The name and batch number of the product
(b) The dates and times of the packaging operations
(c) Identification(initials)of the operator(s) who performed each significant step of the process and where appropriate the name of any person who checked these operations
(d) Records of checks for identity and conformity with packaging instructions including the results of in-process controls
(e) Details of the packaging operations carried out including references to equipment and packaging lines used
(f) Where possible samples of printed packaging materials used including specimens of the batch coding, expiry dating and any additional overprinting
(g) Notes on special problems or unusual events including details with signed authorization for any deviation from the packaging instructions
(h) The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation. Where there are robust electronic controls in place during packaging there may be justification for not including this information.
(i) Approval by the person responsible for the packaging operations

DOCUMENTATION PROCEDURES:

(i) Receipt

There should be written procedures and records for receipt of each delivery of each starting material (including bulk, intermediate or finished goods) primary, secondary and printed packaging materials**.**

Receipt requirements are as follows:

- The name of material on the delivery note and the containers
- The "in-house" name and/or code of the material (if different from above)
- Date of receipt
- Suppliers name and manufacturers name
- Manufacturers batch or reference number
- Total quantity and number of containers received
- The batch number assigned after receipt
- Any relevant comment

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

(ii)Sampling

There should be written procedures for sampling which include the methods and equipment to be used, the amounts to be taken and any precautions to be observed to avoid contamination of the material or any deterioration in its quality

(iii)Testing

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

(iv) Other

- Written, release and rejection procedures should be available for materials and products and in particular for the certification for sale of the finished product by the qualified person(s). All records should be available to the qualified person. A system should be in place to indicate special observation and any changes to critical data
- Records should be maintained for the distribution of each batch of a product in order to facilitate recall of any batch if necessary.
- There should be written policies, procedures, protocols, reports and the associated records of actions taken or conclusions reached where appropriate for the following examples:

-Validation and qualification of processes, equipment and system

-Equipment assembly and calibration

-Technology transfer

-Maintenance, cleaning and sanitation

-Personnel matters including signature lists, training in GMP and technical matters, clothing and hygiene and verification of the effectiveness of training.

-Environmental monitoring

-Pest control

-Complaints

-Recalls

-Returns

-Change control

-Investigations into deviations and non-conformances

-Internal quality/cGMP compliance audits

-Summaries of records where appropriate (eg product quality review)

-Supplier audit

- Clear operating procedures should be available for major items of manufacturing and test equipment
- Logbooks should be kept for major or critical analytical testing, production equipment, and areas where product has been processed. They should be used to record in chronological order as appropriate, any use of the area, equipment/method calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried out these operations. An inventory of documents within the quality management system should be maintained.

3.0 CONTRACT MANUFACTURE AND ANALYSIS

Contract manufacture and analysis must be correctly defined, agreed and controlled to avoid misunderstandings which could result in a product or work of unsatisfactory quality. There must

be a written contract between the contract giver and the contract acceptor which clearly establishes the duties of each party. The contract must clearly state the way in which the qualified person releasing each batch of product for sale exercises his full responsibility.

3.1 The contract giver

The Contract Giver is responsible for assessing the competence of the contract acceptor to carry out successfully the work required and for ensuring by means of the contract that the principles and guidelines of cGMP are followed.

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

The contract Giver should ensure that all processed products and materials delivered to him by the contract acceptor comply with their specifications or that the products have been released by a qualified person.

3.2 The contract acceptor

3.2.1 The contract acceptor must have adequate premises and equipment, knowledge, and experience and competent personnel to carry out satisfactorily the work ordered by the contract giver.

Contract manufacture may be undertaken only by a manufacturer who is the holder of marketing authorization.

3.2.2 The contract acceptor should ensure that all products or materials delivered by him are suitable for the intended purpose.

3.2.3 The contract acceptor should not pass to a third party and any of the work entrusted to him under the contract without the contract givers prior evaluation and approval of the arrangements

3.2.4 Arrangements made between the contract acceptor and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract acceptor.

3.3.5 The contract acceptor should refrain from any activity which may adversely affect the quality of the product manufactured and/or analyzed for the contract giver.

3.3 The contract

3.3.1 A contract should be drawn up between the contract giver and the contract acceptor which specifies their respective responsibilities relating to the manufacture and control of the product. The technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and Good manufacturing practice (GMP). All arrangements for manufacture and analysis must be in accordance with the marketing authorization and agreed by both parties.

3.3.2 The contract must specify the way in which the qualified person releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements for marketing authorization.

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

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

3.3.5 The contract should permit the contract giver to visit the facilities of the contract acceptor

3.3.6 In the case of contract analysis, the contract acceptor should understand that he is subject to inspection by the competent Regulatory Authorities.

4.0 SELF INSPECTION

4.1 Self inspection should be conducted in order to monitor the implementation and compliance to cGMP principles and to propose necessary corrective measures.

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

4.3 Self inspection should be conducted in an independent and detailed way by designated competent persons from the company. Independent audits by external experts may also be useful.

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

4.5. A self-inspection program appropriate to the type of operations of the company, in respect to medicines, ensures compliance with PMPB requirements.

4.6 A comprehensive written procedure that describes the functions of the self-inspection program is available.

4.7 The self-inspection team includes personnel who are suitably trained and qualified in GMP.

4.8 Periodic self-inspections are carried out.

4.9 Reports on the findings of the inspections and on corrective actions are reviewed by appropriate senior company management. Corrective actions are implemented in a timely manner.

5.0 PREMISES

5.1 Buildings in which drugs are manufactured or packaged are located in an environment that, when considered together with measures being taken to protect the manufacturing processes presents a minimal risk of causing any contamination of materials or drugs**.**

5.2 The premises are designed, constructed, and maintained such that they prevent the entry of pests into the building and also prevent the migration of extraneous material from the outside into the building and from one area to another.

5.3 Doors, windows, walls, ceilings, and floors are such that no holes or cracks are evident (other than those intended by design).

5.4 Doors giving direct access to the exterior from manufacturing and packaging areas are used for emergency purposes only. These doors are adequately sealed. Receiving and shipping area(s) do not allow direct access to production areas.

5.5 Production areas are segregated from all non-production areas. Individual manufacturing, packaging, and testing areas are clearly defined and if necessary segregated. Areas where biological, microbiological or radioisotope testing is carried out require special design and containment considerations.

5.6 Laboratory animals' quarters are segregated.

5.7 Engineering, boiler rooms, generators, etc. are isolated from production areas.

5.8 In all areas where raw materials, primary packaging materials, in-process medicines, or medicines are exposed, the following considerations apply to the extent necessary to prevent contamination:

a) Floors, walls, and ceilings permit cleaning. Brick, cement blocks, and other porous materials are sealed. Surface materials that shed particles are avoided.
b) Floors, walls, ceilings, and other surfaces are hard, smooth and free of sharp corners where extraneous material can collect.
c) Joints between walls, ceilings and floors are sealed.

d) Pipes, light fittings, ventilation points and other services do not create surfaces that cannot be cleaned.
e) Floor drains are screened and trapped.
f) Air quality is maintained through dust control, monitoring of pressure differentials between production areas and periodic verification and replacement of air filters. The air handling system is well defined, taking into consideration airflow volume, direction, and velocity. Air handling systems are subject to periodic verification to ensure compliance with their design specifications. Records are kept.
g) Temperature and humidity are controlled to the extent necessary to safeguard materials.
h) Rest, change, wash-up, and toilet facilities are well separated from production areas and are sufficiently spacious, well ventilated, and of a type that permits good sanitary practices.
i) Premises layout is designed to avoid mix-ups and generally optimize the flow of personnel and materials.
j) Working spaces allow the orderly and logical placement of equipment (including parts and tools) and materials.
k) Where physical quarantine areas are used, they are well marked, with access restricted to designated personnel. Where electronic quarantine is used, electronic access is restricted to designated personnel.
l) A separate sampling area is provided for raw materials. If sampling is performed in the storage area, it is conducted in such a way as to prevent contamination or cross-contamination.
m) Working areas are well lit.
n) Utilities and support systems [e.g., Heating, Ventilating, and Air Conditioning (HVAC), dust collection, and supplies of purified water, steam, compressed air, nitrogen, etc.] for buildings in which drugs are manufactured or packaged/labeled are qualified and are subject to periodic verification.
o) Outlets for liquids and gases used in the production of drugs are clearly identified as to their content.
p) Premises are maintained in a good state of repair. Repair and maintenance operations do not affect medicine quality.
q) Where necessary, separate rooms are provided and maintained to protect equipment and associated control systems sensitive to vibration, electrical interference, and contact with excessive moisture or other external factors.
r) Manufacturing equipment must demonstrate that the premises are designed in such a manner that the risk of cross-contamination between products is minimized.
s) Campaign production can be accepted where, on a product by product basis, proper justification is provided, validation is conducted and rigorous validated controls and monitoring are in place and demonstrate the minimization of any risk of cross-contamination.
t) Self-contained facilities are required for:

- Certain classes of highly sensitizing drugs such as penicillins and cephalosporins.
- Other classes of highly potent drugs such as potent steroids, cytotoxics, penicillins or potentially pathogenic drugs (e.g., live vaccines), for which validated cleaning or

inactivation procedures cannot be established (e.g., the acceptable level of residue is below the limit of detection by the best available analytical methods)

- Storage in common areas is allowed once the products are enclosed in their immediate final containers and controls are in place to minimize risks of cross-contamination.
- No production activities of highly toxic non-pharmaceutical materials, such as pesticides and herbicides, are conducted in premises used for the production of drugs.

5.9 Design and construction features of buildings and facilities

1) Any building or buildings used in the manufacture, processing, packing or holding of medicinal products shall be of suitable size, construction and location to facilitate cleaning, maintenance and proper operations.
2) Any such buildings shall have adequate space for the orderly placement of equipment and materials to prevent mix-ups between different components
3) Operations shall be performed within specifically defined areas of adequate size. There shall be separate defined areas or such other control systems for the company's operations as are necessary to prevent contamination or mix-ups during the course of the following procedures:

(a) Receipt, identification, storage and withholding from use of components, medicinal product container, closures and labeling, pending the appropriate sampling, testing or examination by the quality control unit before release for manufacturing or packaging.
(b) Holding rejected components, medicinal product containers, closures and labeling before disposition.
(c) Storage of released components, medicinal product containers, closures and labeling.
(d) Storage of in-process material
(e) Manufacturing and processing operations
(f) Packaging and labeling operations
(g) Quarantine and storage before the release of medicinal products.
(h) Storage of medicinal products after release
(i) Controls and laboratory operations
(j) Aseptic processing which include as appropriate:

- Floors, walls and ceilings of smooth, hard surfaces that are easily cleanable.
- Temperature and humidity controls
- An air supply filtered through high efficiency particulate air(HEPA) filters under positive pressure regardless of whether flow is laminar or non-laminar.
- A system for monitoring environmental conditions
- A system for cleaning and disinfecting the room and equipment to produce aseptic conditions
- A system for maintaining any equipment used to control the aseptic conditions.
- Operations relating to the manufacture, processing and packing of penicillins shall be performed in facilities separate from those used for other drug products for human use.
- Adequate lighting shall be provided in all areas.

5.10 Ventilation, air filtration, air heating and cooling

(a) Adequate ventilation shall be provided
(b) Equipment for adequate control over air pressure, micro-organisms, dust, humidity and temperature shall be provided when appropriate for the manufacture, processing, packing or holding of medicinal products.
(c) Air filtration system including pre-filters and particulate matter air filters shall be used when appropriate on air supplies to production areas.
(d) If air is re-circulated to production areas, measurers shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants.
(e) Air handling systems for the manufacture, processing and packing of penicillins shall be completely separate from those for other medicinal products for human use.

5.11 Plumbing

(a) Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any medicinal product. Potable water shall meet the required standards as per specifications. Water not meeting such standards shall not be permitted in the potable water system.
(b) Drains shall be of adequate size and where connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent back siphonage.

5.12 Sewage and refuse

Sewage, trash and other refuse in and from the building and immediate premises shall be disposed off in a safe and sanitary manner.

5.13 Washing and toilet facilities

Adequate washing facilities shall be provided shall be provided including hot and cold water, soap or detergent, air driers or single service towels and clean toilet facilities easily accessible to working areas.

6.0.0 Equipment

6.1.0 The design, construction and location of equipment permit cleaning, sanitizing, and inspection of the equipment.

6.1.1 Equipment parts that come in contact with raw materials, in-process intermediates or drugs are accessible to cleaning or are removable.

6.1.2 Tanks used in processing liquids and ointments are equipped with fittings that can be dismantled and cleaned. Validated Clean-In-Place (CIP) equipment can be dismantled for periodic verification.

6.1.3 Filter assemblies are designed for easy dismantling.

6.1.4 Equipment is located at a sufficient distance from other equipment and walls to permit cleaning of the equipment and adjacent area.

6.1.5 The base of immovable equipment is adequately sealed along points of contact with the floor.

6.1.6 Equipment is kept clean, dry and protected from contamination when stored.

6.1.7 Equipment does not add extraneous material to the drug.

6.1.8 Surfaces that come in contact with raw materials, in-process intermediates or drugs are smooth and are made of material that is non-toxic, corrosion resistant, non-reactive to the medicines being manufactured or packaged and capable of withstanding repeated cleaning or sanitizing.

6.1.9 The design is such that the possibility of a lubricant or other maintenance material contaminating the drug is minimized.

6.2.0 Equipment made of material that is prone to shed particles or to harbour microorganisms does not come in contact with or contaminate raw materials, in-process medicines..

6.2.1 Chain drives and transmission gears are enclosed or properly covered.

6.2.2 Tanks, hoppers and other similar manufacturing equipment are equipped with covers.

6.2.3 Equipment is operated in a manner that prevents contamination.

6.2.4 Ovens, autoclaves and similar equipment contain only one raw material, in-process medicine or medicine at a time, unless precautions are taken to prevent contamination and mix-ups.

6.2.5 The location of equipment precludes contamination from extraneous materials.

6.2.6 The placement of equipment optimizes the flow of material and minimizes the movement of personnel.

6.2.7 The equipment is located so that production operations undertaken in a common area are compatible and cross-contamination between such operations is prevented.

6.2.7 Fixed pipe work is clearly labeled to indicate the contents and, where applicable, the direction of flow.

6.2.8 Dedicated production equipment is provided where appropriate.

6.2.9 Water purification, storage, and distribution equipment is operated in a manner that will ensure a reliable source of water of the appropriate chemical and microbial purity.

6.3.0 Equipment is maintained in a good state of repair.

6.3.1 Where a potential for contamination during manufacturing or packaging of a medicine exists, surfaces are free from cracks, peeling paint and other defects.

6.3.2 The gaskets are functional.

6.3.3 The use of temporary devices (e.g., tape) is avoided.

6.3.4 Equipment parts that come in contact with medicines are maintained in such a manner that drugs are fabricated or packaged within specifications. Equipment used for significant processing or testing operations is maintained in accordance with a written preventative maintenance program. Maintenance records are kept.

6.3.5 Equipment is designed, located, and maintained to serve its intended purpose.

6.3.6 Measuring devices are of an appropriate range, precision and accuracy. Such equipment is calibrated on a scheduled basis, and corresponding records are kept.

6.3.7 Equipment that is unsuitable for its intended use is removed from manufacture, packaging/labeling, and testing areas. When removal is not feasible unsuitable equipment is clearly labeled as such.

6.3.8 Equipment used during the critical steps of manufacture, packaging/labeling, and testing, including computerized systems, is subject to installation and operational qualification. Equipment qualification is documented.

6.3.9 Equipment used for significant processing and testing operations is calibrated, inspected or checked in accordance with a written program and records are kept.

6.4.0 For equipment used for significant processing or testing operations, usage logs are maintained. These logs should include identification of products, dates of operation, and downtime due to frequent or serious malfunctions or breakdowns. The information should be collected to facilitate the identification of negative performance trends.

7.0 SANITATION

(a) Any building used in the manufacture, processing, packing or holding of medicinal products shall be maintained in a clean and sanitary condition. Any such building shall be free of infestation by rodents, birds, insects and other vermin (other than laboratory animals). Trash and organic waste matter shall be held and disposed off in a timely and sanitary manner.

(b) There shall be written procedures assigning responsibilities for sanitation and describing in sufficient detail the cleaning schedules, methods and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed.

(c) There shall be written procedures for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, medicinal containers, closures, packaging, labeling, materials of medicinal products shall be followed. Rodenticides, insecticides and fungicides shall not be used unless registered and used in accordance with the Pesticides Control Board (PCB).

(d) Sanitation Procedures shall apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations.

(e) Every person who manufactures or packages/labels a drug shall have a written sanitation program available on the premises.

(f) The sanitation program contains procedures that describe the following:

- cleaning requirements applicable to all production areas of the plant with emphasis on manufacturing areas that require special attention;
- requirements applicable to processing equipment;
- cleaning intervals;
- products for cleaning and disinfection, along with their dilution and the equipment to be used;
- the responsibilities of any outside contractor;
- (l)disposal procedures for waste material and debris;
- (m)pest control measures;
- (n)precautions required to prevent contamination of a drug when rodenticides, insecticides, and fumigation agents are used;
- microbial and environmental monitoring procedures with alert and action limits in areas where susceptible products are manufactured or packaged; and
- the personnel responsible for carrying out cleaning procedures.
- The sanitation program is implemented and is effective in preventing unsanitary conditions.
- Cleaning procedures for manufacturing equipment are validated.
- Residues from the cleaning process itself (e.g., detergents, solvents, etc.) are also removed from equipment.
- Evidence is available demonstrating that routine cleaning and storage does not allow microbial proliferation; Where necessary, sanitizers and disinfectants are filtered to remove spores (e.g., isopropyl alcohol).

- Analytical methods used to detect residues or contaminants are validated**.**
- A cleaning procedure requiring complete product removal may not be necessary between batches of the same medicine.

- Individuals who supervise the implementation of the sanitation program;

    - ✓ are qualified by training or experience; and
    - ✓ are directly responsible to a person who has the necessary qualifications .

- (Dusty operations are contained. The use of unit or portable dust collectors is avoided in fabrication areas especially in dispensing, unless the effectiveness of their exhaust filtration is demonstrated and the units are regularly maintained in accordance with written approved procedures.

8.0 HEALTH REQUIREMENTS

a) Minimum health requirements are available in writing.
b) Personnel who have access to any area where a drug is exposed during its manufacture or packaging/labeling must undergo health examinations prior to employment. Medical re-examinations, based on job requirements take place periodically.

   Note: A person who is a known carrier of a disease in a communicable form should not have access to any area where a medicneis exposed. The likelihood of disease transmission by means of a medicinal product would depend on the nature of the disease and the type of work the person carries out. Certain diseases could be transmitted through a medicinalproduct if proper hygiene procedures are not followed by an infected person handling the product. However, a person may also be a carrier of a communicable disease and not be aware of it. Therefore, in addition to strict personal hygiene procedures, systems should be in place to provide an effective barrier that would preclude contamination of the product. These procedures must be followed at all times by all personnel. In the event that an employee is found to be a carrier of a communicable disease, the company should perform a risk assessment to determine if there is any product impact.
c) Employees are instructed to report to their supervisor any health conditions they have that could adversely affect medicinal products.
d) Supervisory checks are conducted to prevent any person who has an apparent illness or open lesions that may adversely affect the quality of drugs from handling exposed raw materials, primary packaging materials, in-process medicines or medicines until the condition is no longer judged to be a risk.
e) When an employee has been absent from the workplace due to an illness that may adversely affect the quality of products, that employee's health is assessed before he or she is allowed to return to the workplace.
f) A procedure in place which describes the actions to be taken in the event that a person who has been handling exposed raw materials, primary packaging materials, in-process medicines or medicines is identified as having a communicable disease.
g) Periodic eye examinations and/or periodic requalification are required for personnel who conduct visual inspections.

h) The written hygiene program clearly defines clothing requirements and hygiene procedures for personnel and visitors.
i) Where a potential for the contamination of a raw material, in-process material or medicine exists, individuals wear clean clothing and protective covering.
j) Direct skin contact is avoided between the operator and raw materials, primary packaging materials, in-process medicines or medicines.
k) Unsanitary practices such as smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines are not permitted in production areas or in any other areas where they might adversely affect product quality.
l) Requirements concerning personal hygiene, with an emphasis on hand hygiene, are outlined and are followed by employees.
m) Requirements concerning cosmetics and jewellery worn by employees are outlined and are observed by employees.
n) Soiled protective garments, if reusable, are stored in separate containers until properly laundered and, if necessary, disinfected or sterilized. A formalized procedure for the washing of protective garments under the control of the company is in place. Washing garments in a domestic setting is unacceptable.
o) Personal hygiene procedures including the use of protective clothing, apply to all persons entering production areas.

9.0 PERSONNEL

1 Key personnel include: the head of production, and the head of quality control and head of quality assurance. Normally key posts should be occupied by full-time personnel. The head of production and quality control must be independent from each other.

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

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

PERSONNEL QUALIFICATIONS

(a) Each person engaged in the manufacture, processing, packing,or holding of a medicinal product shall have education, training and experience or any combination thereof to enable that person to perform the assigned functions. Training shall be in the particular

operations that the employee performs and in current good manufacturing practices(cGMP).Training in current good manufacturing practices shall be conducted by qualified individual on a continuous basis and with sufficient frequency to assure that employees remain familiar with cGMP requirements applicable to them.

(b) Each person responsible for supervising the manufacture, processing, packing or holding of a medicinal product shall have the education, training and experience or any combination thereof to perform assigned functions in such a manner as to provide assurance that the medicinal product has the safety,identity, strength,quality and purity that it purports or is represented to possess.

(c) There shall be an adequate number of qualified personnel to perform and supervise the manufacture,processing,packing or holding of each medicinal product.

PERSONNEL TRAINING

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

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

c) 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.

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

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

9. 9.2 The duties of Qualified person(s) can be summarised as follows:

(a) A Qualified person must ensure that each batch of a medicinal product has been produced and tested/checked in accordance with the directives and the marketing authorization.

(b) For products manufactured outside Malawi, a qualified person must ensure that each imported batch has undergone quality control tests.

(c) A qualified person must certify in a register or equivalent document as operations are carried out and before any release that each production batch satisfies the required standards according to Good Manufacturing Practices.

The responsibilities of Qualified Person(s) may be delegated only to other Qualified Person(s).

9.3 The Head of Production department, generally has the following

responsibilities:

- To ensure that products are produced and stored according to the appropriate documentation inorder to obtain the required quality
- to approve the instructions relating to production operations and to ensure their strict implementation.
- to ensure that production records are evaluated and signed by an authorized person before they are sent to quality control laboratory.
- to check the maintenance of his department, premises and equipment
- to ensure that the appropriate validations are done.
- to ensure that the required initial and continuing training of his departmental personnel is carried out and adapted according to need.

9.4 The Head of Quality Control department, generally has the following

responsibilities:

- To approve or reject as he sees fit, starting materials, packaging materials and intermediates, bulk and finished products
- to evaluate batch records
- to ensure that all necessary testing is carried out
- to approve specifications, sampling instructions, test methods and other

quality control procedures.

- to approve and monitor any contract analysts
- to check the maintenance of his department, premises and equipment.
- to ensure that the appropriate validations are done.
- to ensure that the required initial and continuing training of his

department personnel is carried out and adapted according to need.

Responsibilities of Quality Control Department

(i) A person responsible for making decisions concerning quality control requirements of the manufacturer, packager/labeler, distributor, importer, and wholesaler is on site or fully accessible to the quality control department and has adequate knowledge of on-site operations to fulfill the responsibilities of the position.

(ii)The quality control department has access to adequate facilities, trained personnel, and equipment in order to fulfill its duties and responsibilities.

(iii) Approved written procedures are available for sampling, inspecting, and testing raw materials, packaging materials, in-process drugs, bulk drugs, and finished products.

(iv)Quality control personnel have access to production areas for sampling and investigations as appropriate.

(v) All decisions made by the quality control department are signed and dated by the person in charge of the quality control department or by a designated alternate person.

(vi) The assessment for the release of finished products embraces all relevant factors, including the production conditions, the results of in-process testing, the manufacture and packaging documentation, compliance with the finished product specifications, an examination of the finished package, and if applicable, a review of the storage and transportation conditions.

(vii) Deviations and borderline conformances are evaluated in accordance with a written procedure. The decision and rationale are documented. Where appropriate, batch deviations are subject to trend analysis.

(viii) Any non-conformances, malfunctions or errors including those pertaining to premises, equipment, sanitation, and testing, that may have an impact on the quality and safety of batches pending release or released, should be assessed and the rationale documented.

(ix) The quality control department of the importer/distributor should assure compliance to the current master production documents and the marketing authorization.

(x) The quality control department ensures that raw materials and packaging materials are quarantined, sampled, tested, and released prior to their use in the manufacture or packaging/labeling of a drug.

(xi) Finished products returned from the market are destroyed unless it has been ascertained that their quality is satisfactory. Returned goods may be considered for resale only after they have been assessed in accordance with a written procedure. The reason for the return, the nature of the product, the storage and transportation conditions, the product's condition and history, and the time elapsed since it was originally sold are to be taken into consideration in this assessment. Records of any action taken are maintained.

(xii)Documentation is available to support the rationale to place returned goods into inventory for further resale. (xiii) Rejected materials and products are identified as such and quarantined. They are either returned to the vendors, reprocessed, or destroyed. Actions taken are recorded.

(xiv) The reworking of any lot or batch of drug is given prior approval by the quality control department. Approval of a reworked lot or batch of a medicine by the quality control department is based on documented scientific data, which may include validation. The reworking of products that fail to meet their specifications is undertaken only in exceptional cases. Reworking is permitted only when the following conditions are met:

(a) The quality of the finished product is not affected;

(b)The reworked lot meets specifications;

(c) If it is done in accordance with a defined procedure approved by the quality control department;

(d) All risks have been evaluated;

(e) Complete records of the reworking are kept;

(f) A new batch number is assigned; and

(g) The reworked lot is included in the ongoing stability program.

(h) The reprocessing of any lot or batch of drug is given prior approval by the quality control department. Approval of a reprocessed lot or batch of a drug by the quality control department is based on documented scientific data, which may include validation. The reprocessing of products that fail to meet their specifications is undertaken only in exceptional cases. Reprocessing is permitted only when the following conditions are met:

- The quality of the finished product is not affected;
- The reprocessed lot meets specifications;
- The reprocessing is done in accordance with a defined procedure approved by the quality control department;
- All risks have been evaluated;
- Complete records of the reprocessing are kept;
- A new batch number is assigned; and
- Validation demonstrates that the quality of the finished product is not affected.

(i) Recovery is not considered to be either a reprocessing or a reworking operation.

(j) The need for additional testing of any finished product that has been reprocessed, or reworked, or into which a recovered product has been incorporated, is evaluated and acted on by the quality control department. A record is maintained.

(k)Written agreements for consultants and contract laboratories describe the education, training, and experience of their personnel and the type of services provided and are available for examination and inspection. Records of the activities contracted are maintained.

The quality control department is also responsible for the following:

- All decisions made are signed and dated by the person in charge of the quality control department.
- Establishing and maintaining written agreements clearly describing the respective responsibilities between the manufacturer, the packager/labeler, the distributor, the importer, and the wholesaler relative to any complaint or information that is received respecting the quality of a drug or its deficiencies or hazards.
- Ensuring that guidelines and procedures are in place and implemented for storage and transportation conditions, such as: temperature, humidity, lighting controls, stock rotation, sanitation, and any other precautions necessary to maintain the quality and safe distribution of the drug.
- A description of the shipping configuration and the type of packaging to be employed for shipping the finished product;
- The labeling requirements, including storage conditions and special precautions or warnings, for shipments of the finished product;
- mode(s) of transportation approved for shipping the finished product;
- The verifications required to ensure that no finished product in the shipment has been tampered with and that there are no damaged containers;
- Evidence that shipping requirements (e.g., temperature control) have been met if required; and
- A written agreement clearly describes the respective responsibilities between the manufacturer, the packager/labeler, the distributor, the importer, the wholesaler and the transportation provider relative to the storage and transportation of the drug.
- The sampling of raw materials, packaging materials, in-process drugs, bulk drugs, and finished products is carried out in accordance with detailed written procedures. Samples are representative of the batches of material from which they are taken.
- All complaints and other information concerning potentially defective products are reviewed according to written procedures. The complaint is recorded with all the original details and thoroughly investigated. Appropriate follow-up action is taken after investigation and evaluation of the complaint. All decisions and measures taken as a result of a complaint are recorded and referenced to the corresponding batch records. Complaint records are regularly reviewed for any indication of specific or recurring problems that require attention.
- Establishing a change control system to provide the mechanisms for ongoing process optimization and for assuring a continuing state of control. All changes are properly documented, evaluated, and approved by the quality control department and are identified with the appropriate effective date. Any significant change may necessitate re-validation.
- The tests are performed by a laboratory that meets all relevant GMP requirements.

- Laboratory facilities are designed, equipped, and maintained to conduct the required testing.
- In the microbiology laboratory, environmental monitoring is performed periodically. Microbiological cultures and sample testing are handled in an environment that minimizes contamination.
- The facility used to perform the sterility testing should comply with the microbial limits of an aseptic production facility which should conform to a Grade A within a Grade B background or in an isolator of a Grade A within an appropriate background and limited access to non-essential personnel.
- The individual in charge of the laboratory either
    - *(a)* is an experienced university graduate who holds a degree in a science related to the work being carried out and has practical experience in his or her responsibility area or
    - *(b)* reports to a person who has these qualifications
- Laboratory personnel are sufficient in number and are qualified to carry out the work they undertake.
- Laboratory control equipment and instruments are suited to the testing procedures undertaken. Equipment and records are maintained as per PMPB requirements
- Computerized systems are validated, and spreadsheets are qualified.
- Water used for microbial and analytical tests meets the requirements of the test or assay in which it is used.
- All reagents and culture media are recorded upon receipt or preparation. Reagents made up in the laboratory are prepared according to written procedures and are properly labeled.
- Prepared media are sterilized using validated procedures and stored under controlled temperatures.
- Prepared media are properly labeled with the lot numbers, expiration date and media identification. The expiration date of media is supported by growth-promotion testing results that show the performance of the media still meets acceptance criteria up to the expiration date.
- Sterility and growth-promotion testing are performed to verify the suitability of culture media.
- All purchased ready to use media received are accompanied by a certificate of analysis with expiry date and recommended storage conditions as well as the quality control organisms used in growth-promotion and selectivity testing of that media.
- Procedures are in place to ensure that media are transported under conditions that minimize the loss of moisture and control the temperature.
- Media are stored according to the vendor's instructions.
- Sterility and growth-promotion testing are performed on lots received, unless the vendor is certified. Periodic confirmatory testing is performed for ready to use media received from each certified vendor.
- Records are maintained.
- Reference standards are available in the form of the current reference standards . When such standards have not been established or are unavailable, primary standards can be

used. Secondary standards are verified against reference standard or against the primary standard and are subject to complete confirmatory testing at predetermined intervals. All reference standards are stored and used in a manner that will not adversely affect their quality. Records relating to their testing, storage, and use are maintained.

- Out Of Specification (OOS) test results are investigated to determine the cause of the OOS.
- Procedures are in place to describe the steps to be taken as part of the investigation.
- In the case of a clearly identified laboratory or statistical error, the original results may be invalidated, and the test repeated. The original results should be retained and an explanation recorded.
- When there is no clearly identified laboratory or statistical error and retesting is performed, the number of retests to be performed on the original sample and/or a new sample, and the statistical treatment of the resultant data, are specified in advance in the procedure.
- All valid test results, both passing and suspect, should be reported and considered in batch release decisions.
- If the original OOS result is found to be valid, a deviation is raised against the batch and a complete investigation is conducted. The investigation is performed in accordance to written procedures and should include an assessment of root cause, description of corrective actions and preventive actions carried out and conclusions.
- All arrangements for external testing are in accordance with the marketing authorization for the drug product concerned, including the testing of in-process drugs, intermediates, raw materials, packaging materials and all other necessary testing required .
- There is a written agreement covering all activities of testing between the contract laboratory and the parties involved. The agreement specifies their respective responsibilities relating to all aspects of testing;
- Technical aspects of the agreement are drawn up by qualified personnel suitably knowledgeable in analysis and GMP;
- The agreement permits audit of the facilities and operations of the external laboratory;
- The agreement clearly describes as a minimum who is responsible for:

(i) collection, transportation and storage conditions of samples before testing;

(ii) keeping stability samples at predetermined temperatures and humidity, if applicable;

(iii) testing methods to be used, limits and test method validation; and

(iv) retention of analytical results and supporting documentation

(v) No subcontracting of any work should occur without written authorization.

9.5 The Heads of Production and Quality Control department, generally has some shared or jointly exercised responsibilities relating to quality and

these may include:

- The authorization of written procedures and other documents including

  Amendments

- the monitoring and control of the manufacturing environment
- plant hygiene
- Process validation
- training
- the approval and monitoring of suppliers of materials
- the approval and monitoring of contract manufacturers
- the designation and monitoring of storage conditions for materials and

  Products

- the retention of records
- the monitoring of compliance with the requirements of Good Manufacturing

  Practices(GMP)

9.6 The individual in charge of the quality control department of a

manufacturer, packager/labeler, tester, importer, and distributor; and

the individual in charge of the manufacturing department of a

manufacturer or packager/labeler:

- holds a recognized university degree or a degree recognized as equivalent by PMPB in science related to the work being carried out;
- preferably has five (5) years relevant practical experience in their responsible area;
- directly controls and personally supervises on site, each working shift during which activities under their control are being conducted; and
- may delegate duties and responsibility (e.g., to cover all shifts) to a person in possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a course of study at a university, college or technical institute in a science related to the work being carried out combined with at least two (2) years relevant practical experience, while remaining accountable for those duties and responsibility.

9.7 The individual responsible for packaging operations, including control over printed packaging materials and withdrawal of bulk drugs:

a) is qualified by training and experience; and

b) is directly responsible to the person in charge of the manufacturing department or a person having the same qualifications.

- An adequate number of personnel with the necessary qualifications and practical experience appropriate to their responsibilities are available on site.
- The responsibilities placed on any one individual are not so extensive as to present any risk to quality.
- All responsible personnel have their specific duties recorded in a written description and have adequate authority to carry out their responsibilities.
- When key personnel are absent, qualified personnel are appointed to carry out their duties and functions.
- All personnel are aware of the principles of GMP that affect them, and all personnel receive initial and continuing training relevant to their job responsibilities.
- Training is provided by qualified personnel having regard to the function and in accordance with a written program for all personnel involved in the manufacture of a drug, including technical, maintenance, and cleaning personnel.
- The effectiveness of continuing training is periodically assessed.
- Training is provided prior to implementation of new or revised standard operating procedures (SOPs).
- Records of training are maintained.
- Personnel working in areas where highly active, toxic, infectious, or sensitizing materials are handled are given specific training.
- The performance of all personnel is periodically reviewed.

Other personnel responsibilities

(a) Personnel engaged in manufacturing,processing,packing or labeling of a medicinal product shall wear clean clothing appropriate for the duties they perform. Protective apparel such as head, face, hair and arm coverings shall be worn as necessary to protect medicinal products from contamination.
(b) Personnel shall practice good sanitation and health habits.
(c) Only personnel authorized by supervisory personnel shall enter those areas of the building and facilities designated as limited access areas.
(d) Any person shown at any time(either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of medicinal products shall be excluded from direct contact with components, medicinal products, containers, closures, in-process materials, until the condition is corrected or determined by competent medical personnel not to jeorpadise the safety or quality of medicinal products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on medicinal products.

11.0. TESTING

RAW MATERIAL TESTING

(a) Each raw material used in the production of a drug is covered by specifications that are approved and dated by the person in charge of the quality control department or by a designated alternate.

(b) Specifications are of pharmacopoeal or equivalent status and are in compliance with the current marketing authorization. Where appropriate, additional properties or qualities not addressed by the pharmacopoeia (e.g., particle size, etc.) are included in the specifications.

(c) Where a recognized pharmacopoeia contains a specification for microbial content, that requirement is included.

(d) Purified water that meets the required standards used in the formulation of a non-sterile drug product, unless otherwise required in one of these standards or as stated in the marketing authorization.

(e) Specifications should include requirements for total microbial count, which should not exceed 100 colony forming units (cfu)/ ml.

(f) Purified water should be monitored on a routine basis for the purpose intended to ensure the absence of objectionable microorganisms (e.g., *Escherichia coli* and *Salmonella* for water used for oral preparations, *Staphylococcus aureus* and *Pseudomonas aeruginosa* for water used for topical preparations).

(g) Test methods are validated, and the results of such validation studies are documented. Method transfer studies are conducted when applicable.

(h) A sample of each lot of raw material is fully tested against specifications. Sampling is conducted according to a suitable statistically valid plan.

(i) In addition, each container of a lot of a raw material is tested for the identity of its contents using a specifically discriminating identity test.

(j) In lieu of testing each container for identity, testing a composite sample derived from sampling each container is acceptable, as long as the following conditions are met:

- a suitable test exists;
- the number of individual containers for each composite sample does not exceed ten(10); and
- potency test is performed on each composite sample to establish the mass balance of the composite sample.

(k)In lieu of testing each container for identity, testing only a proportion of the containers is acceptable where evidence is available to ensure that no single container of raw material has been incorrectly labeled.

(l) The available evidence should include an on-site audit report of the vendor, by a person who meets the requirements which address at least the following aspects;

(m) The nature and status of the manufacturer and the supplier and their understanding of the GMP requirements of the pharmaceutical industry;

(n) The Quality Assurance system of the manufacturer of the raw material; and

(o) The manufacturing conditions under which the raw material is produced and controlled.

(p)Where a batch of any raw material, after leaving the site of its manufacture is handled in any substantial way (e.g., repackaged by a third party) prior to its receipt on the premises of the person who formulates the raw material into dosage forms, each container in that batch is sampled and its contents positively identified.

(q)Only raw materials that have been released by the quality control department and that are not past their established re-test date or expiry date are used in manufacturing.

(r) If any raw material is held in storage after the established re-test date, that raw material is quarantined, evaluated, and tested prior to use. The re-test date or expiry date is based on acceptable stability data developed under predefined storage conditions or on any other acceptable evidence. A batch of raw material can be re-tested and used immediately (i.e., within 30 days) after the re-test as long as it continues to comply with the specifications and has not exceeded its expiry date. A raw material held in storage after the established expiry date should not be used in manufacturing.

12.1.1Testing raw material from certified vendors

The testing is performed on a sample taken after receipt of the raw material on the premises of the person who formulates the raw material into dosage form, unless the vendor is certified. A raw material vendor certification program, if employed, is documented in a standard operating procedure. At a minimum, such a program includes the following:

1.1 A written agreement outlining the specific responsibilities of each party involved. The agreement specifies:

1.1.1 The content and the format of the certificate of analysis, which exhibits actual numerical results and makes reference to the raw material specifications and validated test methods used;

1.1.2 That the raw material vendor must inform the manufacturer of any changes in the processing or specifications of the raw material; and

1.1.3 That the raw material vendor must inform the manufacturer in case of any critical deviation during the manufacturing of a particular batch of a raw material.

1.2 An audit report is available.

1.2.1 For medicinal ingredients/active pharmaceutical ingredient (API), the audit report is issued by a qualified authority demonstrating that the API vendor complies with the Good Manufacturing Practices(GMP).

1.3 Complete confirmatory testing is performed on the first three lots of raw material received from a vendor and after significant change to the manufacturing process. A copy of the residual solvent profile is obtained. Additionally, for medicinal ingredients, a copy of the impurity profile is also obtained.

1.4 Identification of how re-testing failures and any subsequent re-qualification of the vendor are to be addressed.

1.5 The list of raw materials not subject to the reduced testing program (e.g., reprocessed lots).

1.6 Complete confirmatory testing is conducted on a minimum of one lot per year of a raw material received from each vendor, with the raw material being selected on a rotational basis.

1.6.1 In addition, where multiple raw materials are received from the same vendor, confirmatory testing is carried out for each raw material at least once every five years.

1.7 A document is issued for each vendor verifying that the vendor meets the criteria for certification. The document is approved by the quality control department and is updated at an appropriate frequency.

12.2. Identity testing:

Specific identity testing is conducted on all lots of any raw material received on the premises of the person who formulates the raw material into dosage forms.

3. Provided that the identity test is performed, the lot of raw material selected for confirmatory testing may be used in manufacture prior to completion of all tests with the approval of the quality control department.

4. Conditions of transportation and storage are such that they prevent alterations to the potency, purity, or physical characteristics of the raw material. In order to demonstrate that these conditions have been met, standard operating procedures and records for shipping and receiving are available and contain:

4.1 the type of immediate packaging for the raw material;

4.2 the labeling requirements including storage conditions and special precautions or warnings, for the packaged raw material;

4.3 the mode(s) of transportation approved for shipping the packaged raw material;

4.4 a description of how the packaged raw material is sealed;

4.5 the verification required to ensure that each package has not been tampered with and that there are no damaged containers; and

4.6 evidence that special shipping requirements (e.g., refrigeration) have been met if required.

5. If a delivery or shipment of raw material is made up of different batches, each batch is considered as separate for the purposes of sampling, testing, and release.

6. If the same batch of raw material is subsequently received, this batch is also considered as separate for the purpose of sampling, testing, and release.

However, full testing to specifications may not be necessary on such a batch provided that all the following conditions are met:

6.1 a specifically discriminating identity test is conducted;

6.2 the raw material has not been repackaged or re-labeled;

6.3 the raw material is within the re-test date assigned by its vendor; and

6.4 evidence is available to demonstrate that all pre-established transportation and storage conditions have been maintained.

Packaging Material Testing

1. Each packaging material used in the packaging/labeling of a drug is covered by specifications that are approved and dated by the person in charge of the quality control department or by a designated alternate who meets the requirements. The use of recycled or reprocessed primary packaging components is permitted only after a full evaluation of the risks involved, including any possible deleterious effects on product integrity. Specific provision is made for such a situation in the specifications.

2. Where applicable, specifications are of pharmacopoeal or equivalent status and are in compliance with the marketing authorization.

3. The adequacy of test or examination methods that are not of pharmacopoeal or equivalent status is established and documented.

4. Only packaging materials released by the quality control department are used in packaging/labeling.

5. Outdated or obsolete packaging material is adequately segregated until its disposition.

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

6.1 Because of the higher risk of using cut labels, these labels are inspected upon receipt for absence of foreign labels using appropriate methods.

7. Sampling should take place in an appropriate environment and with precautions to prevent contamination where necessary.

1.The testing or examination of the packaging material is performed on a sample taken after their receipt on the premises of the person that packages the drug unless the vendor is certified. A packaging material vendor certification program, if employed, is documented in a standard operating procedure. At a minimum, such a program includes the following:

1.1 A written agreement outlines the specific responsibilities of each party involved. The agreement specifies:

1.1.1 all the tests to be performed by the vendor, along with the content and format of the certificate of analysis, which exhibits actual numerical results, if applicable, and makes reference to product specifications;

1.1.2 that the vendor must inform the drug packager/labeler of any changes in the processing or specifications of the packaging material; and

1.1.3 that the vendor must inform the drug packager/labeler of any critical deviations during the manufacturing of a particular batch of a packaging material.

1.2 In lieu of a written agreement, an on-site audit of the vendor's facilities and controls by qualified personnel is acceptable. These audits are performed at an appropriate frequency, and the results are documented;

1.3 The certification procedure also outlines how re-testing failures and any subsequent re-qualification is to be addressed;

1.4 A document is issued for each vendor verifying that the certification criteria have been met. The document is approved by the quality control department and is updated at an appropriate frequency;

1.5 When a certification program is implemented, complete confirmatory examination or testing of a minimum of one lot per year per vendor is required for non-printed packaging material; and

1.6 Generally, due to the nature of its operations, a broker or wholesaler of packaging materials cannot be directly certified. However, when a broker or wholesaler supplies materials received from the original vendor without changing the existing labels, packaging, certificate of analysis, and general information, then certification of the original source is still acceptable.

2. Provided that the material is properly identified, the lot of packaging material selected for confirmatory testing may, with the approval of the quality control department, be used in packaging prior to completion of that testing.

3. Conditions of transportation and storage are such that they prevent alterations of the characteristics of the packaging material. In order to demonstrate that these conditions have been met, standard operating procedures and records are available and contain the following:

3.1 the type of packaging to be employed;

3.2 labeling requirements;

3.3 mode of transportation;

3.4 the type of seal used on the package; and

3.5 the verification required to ensure that the package has not been tampered with and that there are no damaged containers.

4. Positive identification of all packaging materials, along with examination of all labels and other printed packaging materials, is conducted following their receipt on the premises of the person who packages the drug.

5. If a delivery or shipment of packaging material is made up of different batches, each batch is considered as separate for the purposes of sampling, testing, and release.

16.0 Finished Product Testing

(i)Written specifications are approved by the person in charge of the quality control department or by a designated alternate who meets PMPB requirements

(ii) The written specifications contain a description of the drug in dosage form. This description includes all properties and qualities, including physical characteristics, identity, purity, and potency. The specifications also include tolerances and a description of all tests used to measure compliance with the established tolerances, in sufficient detail to permit performance by qualified personnel. When a unique identifier is used for identity testing, it is described in the specifications.

(iii)Specifications are equal to or exceed a recognized standard and are in compliance with the marketing authorization.

(iv) Where a recognized pharmacopoeia contains a specification for microbial content, that requirement is included.

(v) Test methods are validated, and the results of such validation studies are documented. Method transfer studies are conducted when applicable.

(vi)All tests are performed according to the approved specifications. These tests may be carried out by the distributor or by their contracted testing laboratory when a written agreement specifically excludes the manufacturer from this obligation.

(vii)Any lot or batch of a drug that does not comply with specifications is quarantined pending final disposition and is not made available for sale.

(viii) Identity is confirmed by the packager/labeler after the lot or batch is packaged.

18.0 Samples:

(a) A sample of each lot or batch of a finished product is retained by the distributor and by the importer of the drug.

(b)Retention samples are kept in their trade package, or in a container that is equivalent with respect to stability. In the case of large containers of finished products, a smaller representative sample may be retained, as supported by stability data. This allowance does not apply to sterile products.

(c) Retention samples are stored under the conditions indicated on the label.

(d) Retention samples are maintained in accordance with a written procedure.

(e) A sample of each lot or batch of a raw material (including both active and inactive ingredients), is retained by the manufacturer of the medicine.

(f) The sample is stored in the same packaging system in which the raw material is stored or in one that is equivalent to or more protective than the vendor's packaging system of the raw material.

(g) The sample is stored under the conditions recommended by the vendor.

(h)Retention samples are maintained in accordance with a written procedure.

(i). In determining the size of sample to be maintained, it is to be kept in mind that PMPB needs at least enough of the material to carry out tests to determine whether the medicine or the raw

material complies with its specifications. The manufacturer, distributor, or importer may also wish to test the material in the event of a complaint; the sample should therefore be at least double the amount needed to complete all required tests.

(j) This requirement is not considered to be applicable to the number of units normally required for sterility and pyrogen testing.

19.0 Stability

(i) The stability of the drug is determined prior to marketing and prior to adoption of significant changes in formulation, fabrication procedures, or packaging materials that may affect the shelf life of the drug. This determination is made in accordance with PMPB guidelines, which include conditions for storage of stability samples.

(ii)Accelerated stability data are considered to be preliminary information only. The accelerated data are supported by long term testing. When the shelf-life is assigned based on accelerated data and extrapolated long-term data, it should be verified by additional long term stability data as these data become available.

(iii)Stability studies are carried out on the drug in each package type in which it is to be sold .

(iv) For new drugs, at least three commercial-scale batches of each strength are sampled to verify or confirm shelf life post-approval, unless such data are submitted as a part of the application for marketing approval. For existing drugs (e.g., generic drugs), two commercial-scale batches of each strength are sampled. The principle of bracketing and matrixing designs may be applied if justified.

(v) For imported products, stability studies originating from foreign sites are acceptable provided that the data meet the requirements of PMPB guidelines regarding stability and that the site can demonstrate GMP compliance.

(vi) The shelf life is established based on the date of manufacture.

(vii)Stability data are available for drugs before and after constitution, reconstitution or dilution, if applicable.

(viii) Analytical test procedures used in stability evaluation are validated in accordance with PMPB requirements: Assays are to be stability-indicating, (e.g., sufficiently specific to detect and quantify degradation products and to distinguish between degraded and non-degraded materials). Limits for individual specified, unspecified, and total degradation products are included.

(ix) A continuing stability program is implemented to ensure compliance with the approved shelf life specifications. A protocol is available and is implemented for each drug marketed in Malawi.

A summary of all the data generated, including the evaluation and the conclusions of the study, is prepared. This program includes but is not limited to the following parameters:

- reference to the manufacturing master formula and the packaging master formula

- number of batch(es) per strength, packaging, and batch sizes,

- relevant physical, chemical, microbiological or biological test methods,

- acceptance criteria,

- container closure system(s),

- testing frequency,

- storage conditions (and tolerances) of samples

- orientation of samples reflective of the worst-case scenario, and

- other applicable parameters specific to the drug.

2.Any differences in the protocol for the continuing stability program and the protocol for the formal stability studies are scientifically justified.

3. A minimum of one batch of every strength and container closure system of the drug is enrolled into the continuing stability program each year the drug is produced. The principle of bracketing and matrixing designs may be applied if justified.

4. Worst case situations should be addressed by the continuing stability program (e.g., inclusion of reworked or reprocessed lots).

5.Any confirmed out of specification result, or significant negative trend that may have an impact on the quality of the product should be assessed and may require further stability studies.

6. For imported products, stability studies originating from foreign sites are acceptable, provided that the data meet the requirements of PMPB guidelines regarding stability and that the site can demonstrate GMP compliance. It is the importer's responsibility to obtain and maintain up to date records associated with the ongoing stability program

13.0 MANUFACTURING CONTROL

(a) All handling of raw materials, products, and packaging materials such as receipt, quarantine, sampling, storage, tracking, labeling, dispensing, processing, packaging and distribution is done in accordance with pre-approved written procedures or instructions and recorded.

(b) All critical production processes are validated. Detailed information is provided in various PMPB validation guidelines.

(c) Validation studies are conducted in accordance with predefined protocols. A written report summarizing recorded results and conclusions is prepared, evaluated, approved, and maintained.

(d) Changes to production processes, systems, equipment, or materials that may affect product quality and/or process reproducibility are validated prior to implementation.

(e) Any deviation from instructions or procedures is avoided. If deviations occur, qualified personnel investigate, and write a report that describes the deviation, the investigation, the rationale for disposition, and any follow-up activities required. The report is approved by the quality control department and records maintained.

(f) Checks on yields and reconciliation of quantities are carried out at appropriate stages of the process to ensure that yields are within acceptable limits.

(g) Deviations from the expected yield are recorded and investigated.

(h) Access to production areas is restricted to designated personnel.

(i) Before any processing operation is started, steps are taken and documented 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.

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

(k) Checks should be carried out to ensure that transfer lines and other pieces of equipment used for the transfer of products from one area to another are correctly connected.

(l) At every stage of processing, products and materials are appropriately protected from microbial and other contamination.

(m) In-process control activities that are performed within the production areas do not pose any risk to the quality of the product.

(n) Measuring devices are regularly checked for accuracy and precision, and records of such checks are maintained.

(o) At all times during processing, all materials, bulk containers, major items of equipment and the rooms used are labeled or otherwise identified with an indication of the product or material being processed, its strength, and the batch number and, if appropriate, the stage of manufacturing.

(p) Rejected materials and products are clearly marked as such and are either stored separately in restricted areas or controlled by a system that ensures that they are either returned to their vendors or, where appropriate, reprocessed or destroyed. Actions taken are recorded.

(q) Upon receipt, raw materials, packaging materials, in-process (intermediate) drugs, and bulk drugs, are accounted for, documented, labeled and held in quarantine until released by the quality control department.

(r) Procedures are in place to ensure the identity of the contents of each container. Containers from which samples have been drawn are identified.

(s) For each consignment, all containers are checked for integrity of package and seal and to verify that the information on the order, the delivery note and the vendor's labels is in agreement.

(t) Damage to containers, along with any other problem that might adversely affect the quality of a material, is recorded, reported to the quality control department, and investigated.

(u) Upon receipt, containers are cleaned where necessary and labeled with the prescribed data.

(v) Labels for bulk drugs, in-process drugs, raw materials, and packaging materials bear the following information:

(w) the designated name and, if applicable, the code or reference number of the material;

(x) the specific batch number(s) given by the vendor and on receipt by the manufacturer or packager/labeler;

(xi) the status of the contents (e.g., in quarantine, on test, released, rejected, to be returned or recalled) appears on the label when a manual system is used;

(xii) an expiry date or a date beyond which re-testing is necessary; and

(xiii) the stage of manufacturing of in-process material, if applicable.

Note: When fully computerized storage systems are used, backup systems are available in case of system failure to satisfy the requirements..

(xiv) Raw materials are dispensed and verified by qualified personnel, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labeled containers. Raw materials which are being staged are properly sealed and stored under conditions consistent with the accepted storage conditions for that material.

Manufacturing Master Formula

(i) Processing operations are covered by master formula that are prepared by, and are subject to independent checks by, persons who have the necessary qualifications including the quality control department.

(ii) Master formula are written to provide not less than 100% of label claim. Overages may be allowed to compensate for processing losses with documented justification and approval if appropriate. In exceptional instances, overages to compensate for losses due to degradation during manufacturing or shelf-life must be scientifically justified and in accordance with the marketing authorization. Master formula also include the following:

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

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

(c) a list of all raw materials to be used, along with the amount of each, described using the designated name and a reference that is unique to that material (mention is made of any processing aids that may not be present in the final product);

(d)a statement of the expected final yield, along with the acceptable limits, and of relevant intermediate yields, where applicable;

(e)identification of the principal equipment to be used, and if applicable internal codes;

(f) the procedures, or reference to the procedures, to be used for preparing the critical equipment, (e.g., cleaning, assembling, calibrating, sterilizing, etc.);

(g) detailed stepwise processing instructions (e.g., checks on materials, pre-treatment, sequence for adding materials, mixing times or temperatures, etc.);

(h) the instructions for any in-process controls, along with their limits; and

(i) where necessary, the requirements for storage of the products and in-process materials, including the container-closure system, labeling storage conditions, maximum validated hold time, and any special precautions to be observed.

Packaging Master Formula

(i) In the case of a packaged product, the master formula also includes for each product, package size and type, the following:

(ii) the package size, expressed in terms of the number, weight, or volume of the product in the final container;

(iii) 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;

(iv) 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 are to be positioned;

(v) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before operations begin. These verifications are recorded;

(vi) a description of the packaging operations, including any significant subsidiary operations and the equipment to be used; and

(vii) details of in-process controls, with instructions for sampling and acceptance limits**.**

Manufacturing Operations

(i) Each batch processed is effectively governed by an individually numbered manufacturing order prepared by qualified personnel from the master formula by such means as to prevent errors in copying or calculation and verified by qualified personnel.

(ii) As it becomes available during the process, the following information is included on or with the manufacturing batch record:

(a) the name of the product;

(b) the number of the batch being manufactured;

(c) dates and times of commencement and completion of significant intermediate stages, such as blending, heating, etc., and of production;

(d)the batch number and/or analytical control number, as well as the quantity of each raw material actually weighed and dispensed (for active raw material, the quantity is to be adjusted if the assay value is less than 98% calculated on "as is" basis and on which the master formula was based);

(e) confirmation by qualified personnel of each ingredient added to a batch;

(f) the identification of personnel performing each step of the process; and of the person who checked each of these steps;

(g) the actual results of the in-process quality checks performed at appropriate stages of the process and the identification of the person carrying them out;

(i) the actual yield of the batch at appropriate stages of processing and the actual final yields, together with explanations for any deviations from the expected yield;

(j)detailed notes on special problems with written approval for any deviation from the master formula; and

(k)after completion, the signature of the person responsible for the processing operations. Batches are combined only with the approval of the quality control department and according to pre-established written procedures.

(l)Batches are combined only with the approval of the quality control department and according to pre-established written procedures.

(m) The introduction of part of a previous batch, conforming to the required quality, into the next batch of the same product at a defined stage of fabrication is approved beforehand. This recovery is carried out in accordance with a validated procedure and is recorded.

14.0 Packaging Operations

(a) Packaging operations are performed according to comprehensive and detailed written operating procedures or specifications, which include the identification of equipment and packaging lines used to package the drug, the adequate separation and if necessary, the dedication of packaging lines that are packaging different drugs and disposal procedures for unused printed packaging materials. Packaging orders are individually numbered.

(b)The method of preparing packaging orders is designed to avoid transcription errors.

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

(d) All products and packaging materials to be used are checked on receipt by the packaging department for quantity, identity and conformity with the packaging instructions.

(e)Precautions are taken to ensure that containers to be filled are free from contamination with extraneous material.

(f)The name and batch number of the product being handled is displayed at each packaging station or line.

(g)Packaging orders include the following information (recorded at the time each action is taken):

(h) the date(s) and time(s) of the packaging operations;

(i) the name of the product, the batch number, packaging line used, and the quantity of bulk product to be packaged, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;

(j) the identification of the personnel who are supervising packaging operations and the withdrawal of bulks;

(k) the identification of the operators of the different significant steps;

(l) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;

(m) the general appearance of the packages;

(n) whether the packages are complete;

(o) whether the correct products and packaging materials are used;

(p) whether any on-line printing is correct;

(q)the correct functioning of line monitors;

(r)handling precautions applied to a partly packaged product;

(s) notes on any special problems, including details of any deviation from the packaging instructions with written approval by qualified personnel;

(t) the quantity, lot number, and/or analytical control number of each packaging material and bulk drug issued for use; and

(u) a reconciliation of the quantity of printed packaging material and bulk drug used, destroyed or returned to stock.

(v) To prevent mix-ups, samples taken away from the packaging line are not returned.

(w)Whenever possible, samples of the printed packaging materials used, including specimens bearing the batch number, expiry date, and any additional overprinting, are attached to packaging orders.

(x) Filling and sealing are followed as quickly as possible by labeling. If labeling is delayed, procedures are applied to ensure that no mix-ups or mislabeling can occur.

(xi). Upon completion of the packaging operation, any unused batch-coded packaging materials are destroyed, and their destruction is recorded. A procedure is followed if non-coded printed materials are returned to stock.

(xii) Outdated or obsolete packaging materials are destroyed and their disposal is recorded.

(xiii)Products that have been involved in non-standard occurrences during packaging are subject to inspection and investigation by qualified personnel. A detailed record is kept of this operation.

(xiv) Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units packaged is investigated and satisfactorily accounted for before release. Validated electronic verification of all printed packaging materials on the packaging line may obviate the need for their full reconciliation.

(xv)Printed packaging materials are:

(a) stored in an area to which access is restricted to designated personnel who are supervised by persons who have the required qualifications.
(b) withdrawn against a packaging order;
(c) issued and checked by persons who have the required qualifications
(d) identified in such a way as to be distinguishable during the packaging operations.

(xvi)To prevent mix-ups, roll-fed labels are preferred to cut labels. Gang printing (printing more than one item of labeling on a sheet of material) is avoided.

(xvii) Cut labels, cartons, and other loose printed materials are stored and transported in separate closed containers.

(xviii) Special care is taken when cut labels are used, when overprinting is carried out off-line and in hand-packaging operations. On line verification of all labels by automated electronic means can be helpful in preventing mix-ups. Checks are made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

(xix)The correct performance of any printing (e.g., of code numbers or expiry dates) done separately or in the course of the packaging is checked and recorded.

(xx)Raw materials, packaging materials, intermediates, bulk drugs and finished products are *(a)* stored in locations that are separate and removed from immediate manufacturing areas, and *(b)* transported under conditions designated by the quality control department to preserve their quality and safety.

(xxi)All intermediate and finished products are held in quarantine,until released by the quality control department.

(xxii) Every package of a drug is identified by a lot number.

15.0 Annual Product Review

(i) Regular periodic or rolling quality reviews of all medicnes, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both raw materials and finished product to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least:

(ii) A review of critical in-process controls, finished product testing results and specifications.

(iii)A review of all batches that failed to meet established specification(s) and their investigation.

(iv) A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.

(v) A review of all changes carried out to the processes, analytical methods, raw materials, packaging materials, or critical suppliers.

(vi)A review of the results of the continuing stability program and any adverse trends.

(vii) A review of all quality-related returns, complaints and recalls and the investigations performed at the time.

(viii) A review of adequacy of any previous corrective actions related to product process, or equipment.

(ix) The qualification status of relevant equipment and systems (e.g., HVAC, water, compressed gases, etc.); and

(x) A review of agreements to ensure that they are up to date.

(xi) Quality reviews may be grouped by product type (e.g., solid dosage forms, liquid dosage forms, sterile products, etc. where scientifically justified).

(xii) The quality control department of the importer or distributor should ensure that the annual product quality review is performed in a timely manner.

(xiii) Where required, there should be an agreement in place between the various parties involved (e.g., importer and manufacturer) that defines their respective responsibilities in producing and assessing the quality review and taking any subsequent corrective and preventative actions.

(xiv) The quality control department should evaluate the results of this review and an assessment should be made whether corrective and preventative action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventative actions should be completed in a timely and effective manner. There should be

procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection.

Recall system

A written recall system is in place to ensure compliance with PMPB guidelines and requires the following:

5 PMPB is to be notified of the recall;
6 Action that is taken to recall a product suspected or known to be in violation is prompt and in accordance with a pre-determined plan;the procedures to be followed are in writing and are known to all concerned.
7 The person(s) responsible for initiating and co-ordinating all recall activities are identified;
8 The recall procedure is capable of being put into operation at any time, during and outside normal working hours;
9 The recall procedure outlines the means of notifying and implementing a recall and of deciding its extent;
10 Distribution records enable tracing of each medicinal product, and account is taken of any products that are in transit, any samples that have been removed by the quality control department, and any professional samples that have been distributed;
11 Wholesalers must obtain drug products from companies that hold an establishment licence as required by PMPB in order to facilitate a system of control that permits complete and rapid recall;
12 A written agreement clearly describes respective responsibilities when the importer or distributor assumes some or all of the wholesaler's responsibilities with respect to recalls;
13 Recalled products are identified and are stored separately in a secure area until their disposition is determined;
14 The progress and efficacy of the recall is assessed and recorded at intervals, and a final report is issued (including a final reconciliation); and
15 All establishments involved in the manufacture, distribution, or importation of the recalled product are notified.

PART TWO : STERILE PRODUCTS

A drug that is intended to be sterile shall be manufactured and labeled:

(a) In separate and enclosed area

(b) Under supervision by personnel trained in microbiology

(c) By a method scientifically proven to ensure sterility

There are basic differences between production of sterile medicinal products using aseptic processing and production using terminal production. Terminal sterilization usually involves filling and sealing product containers under high quality environmental conditions. Products are filled and sealed in this type of environment to minimise microbial and particulate content of in-process product and to help ensure that the subsequent sterilization process is successful. In most cases the product container and closure has low bio-burden but they are not sterile. The product in its final container is then subjected to a sterilization process such as heat and irradiation**.**

Note: In aseptic process the medicinal product, container and closure are first subjected to sterilization methods separately, as appropriate and then brought together. Because there is no process to sterilize the product in its final container, it is critical that the containers be filled and sealed in an extremely high quality environment.

(i) When designing procedures for achieving sterility, a number of factors must be considered, particularly airborne microorganisms, particulate matter, the size of the opening of the container, the length of time contents are exposed, and assurance that all the material is exposed to the sterilization condition or process.

(ii) All aqueous-based sterile products must be subjected to terminal steam sterilization, with the following exceptions:

- Instances where terminal steam sterilization is not practicable (e.g., where the sterilization process would cause product or packaging degradation). The rationale for the departure from the standard is fully evaluated and documented; and
- Aseptic processes that exclude human intervention (e.g., robotics, form-fill-seal, and barrier systems) may be employed in lieu of terminal sterilization, provided that the data developed demonstrate an acceptable level of sterility assurance. Any such methods introduced are fully validated, taking into account all critical factors of the technology used as well as the routine monitoring to be carried out.

20.1.0 Drugs subject to terminal sterilization

(i) Formulation takes place in an environment with a minimum classification of Grade C, provided that the formulated bulk is immediately subjected to its subsequent processing step, (e.g., filtration, sterilization), in order to minimize bio-burden and particulates.

(ii)Formulation may take place in a Grade D environment if additional measures (e.g., the use of closed systems of manufacture) are taken to minimize contamination.

(iii) Parenterals are filled in an aseptic area with at least a Grade B environment or in a Grade A zone with at least a Grade C background, before terminal sterilization.

(iv) Parenterals that are to be terminally sterilized may be filled in a Grade C area if the process or product does not pose a high-risk of microbial contamination. Examples of high-risk situations include slow filling operations, the use of wide-necked containers, or the exposure of filled containers to the environment for more than a few seconds before sealing.

(v) Non-parenterals may be filled in a Grade C environment before terminal sterilization.

20.1.1 Drugs not subject to terminal sterilization

(i) Parenterals sterilized by filtration, are formulated in an environment with a minimum classification of a Grade C.

(ii) Non-parenteral products may be formulated in a Grade D environment if additional measures are taken to minimize contamination, such as the use of closed systems.

(iii) Sterile filtration requires a minimum filter rating of 0.2 µm. The integrity of the filter is verified before and after use by an appropriate method such as a bubble point, diffusion or pressure hold tests.

(iv) Filling operations are performed under local Grade A conditions within a Grade B background environment. However a lower-grade background environment may be acceptable if specialized automated or barrier techniques are employed and if those techniques are validated to demonstrate that their use has no negative impact on the quality of the drug.

20.1.2 Medicines not subject to filtration or terminal sterilization

(i) Sterile products subject to neither filtration nor terminal sterilization, are produced from sterile raw materials and packaging components in an aseptic area under local Grade A conditions with a Grade B background.

(ii) The air standards described in the following tables are to be achieved throughout the area when it is occupied and in operation. In the operational condition for Grade A zone, the air standards apply in the zone immediately surrounding the drug whenever it is exposed, and with at least a Grade B background. It may not always be possible to demonstrate conformity with air standards for non-viable particulates at the point of fill when filling is in progress, owing to the generation of particles or droplets by the product itself.

(iii) The "at rest" state is the condition where the installation is complete, including manufacturing equipment installed and present in an operational condition but not in use and with operating personnel absent. The "in operation" state should not commence until all the predefined criteria have been met with the equipment and personnel in place.

(iv)The classification of aseptic and clean areas is based on environmental results obtained using acceptable standardized air sampling methods. Such methods take into account the volume and number of samples taken at each location and the total number of sampling locations. The number of sampling locations is based on room volume and on the nature of the operations being undertaken. Sampling methods used during the operational state do not interfere with zone protection.

(v)Radiation sterilization is used mainly for heat-sensitive materials. Since drugs and packaging materials are radiation-sensitive, this method is permissible only when, prior to use, evidence has confirmed the absence of any damaging effects on the material.

(vi)Ethylene Oxide sterilization is used only when other methods are not practicable. Evidence must be available to show the absence of any damaging effect on the drug when this method is used. The conditions and time allowed for degassing the drug are such that residual gas and reaction products are reduced to clearly defined acceptable limits.

(vii) Ultraviolet irradiation is not an acceptable method of sterilization.

(viii) Basic environmental standards for manufacture of sterile products:

	At rest(note 5)		**In operation**	
Grade	**Max permitted number of particles/m3 equal to or above (note 3)**			
	0.5 µm	5 µm	0.5 µm	5 µm
A (Note 1)	3 520	20	3 520	20
B (Note 2)	3 520	29	352 000	2 900
C (Note 2)	352 000	2 900	3 520 000	29 000
D (Note 2)	3 520 000	29 000	not defined (Note 4)	not defined (Note 4)

Notes:

(1)Unidirectional airflow systems provide a homogeneous air speed of 0.45 meters/ second +/- 20% (guidance value) at the working position in open clean room applications. The maintenance of unidirectional air flow should be demonstrated and validated. A unidirectional air flow and lower velocities may be used in closed isolators and glove boxes.

(2)In order to attain air Grades B, C, and D, the number of air changes will be related to the size of the area and to the equipment and personnel present in the area.

(3)Low values for contaminants are reliable only when a large number of air samples are taken. Adequate data is available to generate confidence that the required conditions are met throughout the duration of the operations.

(4)The requirement and limits for this area will depend on the nature of the operations carried out.

(5)The particulate conditions given in the "at rest" column are to be achieved after a short clean-up period (15 to 20 minutes) in an unmanned state after completion of operations.

Chart 1.0: Recommended limits for microbial contamination

Recommended limits for microbial contamination (refer to Note a and e)				
Grade	Air sample Colony forming units Cfu/m^3	Settle plates(diameter 90mm),colony forming units(cfu)/4 hours(refer to note b)	Contact plates(diameter 55mm),colony-forming units(cfu)/plate (refer to note c	Glove print(5 fingers) colony-forming units(cfu)/glove(refer to note d)
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Notes:

(a)These are average values; however, averaging of results can mask unacceptable localized conditions, therefore individual excursions should be treated with caution. Appropriate alert and action limits should be set for microbial monitoring. If the limits are exceeded, operating procedures should prescribe investigation and corrective action. Samples from Grade A critical area environments should normally yield no microbial contaminants.

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

(c)The surface sampled with a contact plate is subject to appropriate cleaning immediately after use.

(d)Monitoring is conducted after critical operations are complete.

(e)All indicated sampling methods are required unless alternative methods demonstrate equivalency.

20.1.4 Premises

(i) To the extent possible, premises are designed to avoid the unnecessary entry of supervisory or control personnel. Grade B areas are designed so that all critical operations can be observed from outside.

(ii)To prevent the shedding or accumulation of dust and other particulate matter, ceilings, floors, and walls in aseptic areas, and floors and walls in clean areas, have smooth impervious surfaces that permit the repeated application of cleaning and disinfecting agents.

(iii) To reduce the accumulation of dust and to facilitate cleaning, projecting ledges or shelves and electrical and mechanical equipment are kept to a minimum. Covings are required where walls meet floors or ceilings. Walls, floors, and ceilings form an effective seal around any traversing pipe or duct.

(iv) False ceilings are sealed to prevent contamination from the space above them.

(v) Un cleanable devices, such as certain sliding-door rails, are avoided.

(vi) Where required, sinks and drains are designed, located, and maintained so as to minimize risks of microbial contamination. Sinks and drains are excluded from areas where aseptic operations are carried out.

(vii)Hand-washing facilities are provided only in changing rooms.

(viii) Changing rooms are designed as airlocks and are used to separate the different stages of changing, thus minimizing microbial and particulate contamination of protective clothing. They are effectively flushed with filtered air. In the final stage, they are, at rest, the same grade as the area into which they lead.

(ix). Access to clean and aseptic areas is provided only through air-locks. Doors to airlocks are arranged so that, either by design or by procedure, only one side or door may be opened at one time (except for emergencies).

(x). The air for clean and aseptic areas is supplied through filters of suitable efficiency. Unidirectional air flow systems are of appropriate design.

(xi) The filtered air supply for clean and aseptic areas is designed to provide a manufacturing environment that meets the required grade classifications. Under all operational conditions, a positive pressure of filtered airflow is maintained in relation to surrounding areas of a lower grade. Particular attention is paid to protecting critical areas, that is, the immediate environment in which the sterilized drug product, containers, and closures are exposed.

(xii) The air system should be provided with appropriate terminal filters such as high-efficiency particulate air (HEPA) for Grades A, B and C. An intact HEPA filter should be capable of retaining at least 99.97% of particulates greater than 0.3 µm in diameter.

(xiii)In Grade A areas the air velocity should be sufficient to protect exposed product, product contact components and product contact surfaces from environmental contamination, by sweeping particles away from the filling/closing area and maintain a unidirectional airflow during operations. Air velocity measurements should be taken at locations where meaningful and reproducible results can be obtained. Such locations should normally be not more than 30 cm away from the work site, within the air flow.

(xiv) In "critical areas" HEPA filters should be leak tested at least twice a year. The purpose of performing regularly scheduled leak tests is to detect leaks from the filter media, filter frame or seal. The aerosol selected for HEPA leak testing should not support microbial growth and should be composed of a sufficient number of particles at approximately 0.3 µm.

(xv)HEPA filtered air should be supplied in critical areas at a velocity sufficient to sweep particles away from the filling/ closing area and maintaining a unidirectional airflow. In situ air pattern analysis should be conducted at the critical area to demonstrate unidirectional air flow, sweeping action over and away from the product, and the absence of turbulence or eddy currents.

(xvi) For aseptically filled products, the transportation and loading of partially sealed containers, such as between filling and lyophilization, should be under Grade A conditions.

(xvii). Warning systems alert personnel when air pressure or airflow falls below established limits. Pressure differentials between areas are monitored and recorded where such differences are of importance.

(xviii)Pressure differentials between 10 and 15 Pa (0.10 cm and 0.15 cm or 0.04" and 0.06" of water) are considered effective between zones of different environmental classifications.

(xix)Pressure differentials between aseptic areas and adjacent areas should be monitored continuously and documented. All alarms should be documented and deviations from established limits should be investigated. When doors are open, outward air flow should be sufficient to minimize ingress of contamination. It is critical that the time the door can remain ajar be strictly controlled.

(xx) Airflow patterns do not present a contamination risk. For example, care is taken to ensure that airflows do not distribute particles from a particle-generating person, operation, or machine to a zone of higher product risk.

(xxi) All work with microorganisms and other infectious agents known to require special precautions in manipulation is safely segregated.

20.1.5 Equipment

(i) Equipment is designed in such a way as to facilitate cleaning, disinfection, or sterilization. Electronic accessories and those parts of large equipment that are not readily amenable to such treatment are appropriately and adequately sealed or effectively isolated.

(ii) To the extent possible, equipment fittings and services are designed and installed so that operations, maintenance, and repairs can take place outside clean or aseptic areas.

(iii) When equipment maintenance is carried out within aseptic areas during operations, sterilized instruments and tools are used. If the required standards of cleanliness and/or asepsis are not maintained during the maintenance work, the area is cleaned and disinfected before processing recommences.

(iv) All equipment, including sterilizers, air-filtration systems, and water-treatment systems, are subject to planned maintenance, validation, and monitoring. Following maintenance/validation, the approval for use of the equipment is documented.

(v)For aseptically filled products, conveyor belts do not pass through a partition from a Grade A or Grade B area to an area of lower cleanliness unless the belts are continuously sterilized (e.g., they pass through a sterilizing tunnel).

(vi) Vent filters used on equipment directly involved in aseptic filling such as receiving tanks, transfer lines, and surge vessels should be integrity tested upon installation where practical or prior to installation and after batch completion.

(vii). Vent filters used on stationary equipment such as Water for Injection (WFI) storage tanks and sterilizers, and membrane filters used to filter compressed gases, should be integrity tested prior to installation and periodically there after.

(viii). Filter integrity test failures should be investigated. Filters should be replaced according to written criteria at appropriate, predefined intervals, and documented.

(ix)All critical surfaces that come in direct contact with sterile materials should be sterile.

20.1.6 Water Treatment Systems

(i) Water treatment facilities are designed, constructed, and maintained so as to ensure the reliable production of water of an appropriate quality. They are not operated beyond their designed capacity. Water is produced, stored, and distributed in a manner that minimizes microbial growth and prevents other types of contamination.

(ii) The quality of the raw feed water is established by specification and is periodically monitored for compliance. The sampling plan takes seasonal variations into account. Records are maintained.

(iii) Purified water is used as feed water for WFI systems and for clean steam generators. WFI is produced either by distillation or by reverse osmosis.

(iv) WFI is used in the formulation of parenteral, irrigation, and intra-ocular products. Purified water may be used in the formulation of ophthalmic products.

(v) Purified water and WFI systems are validated that is, the ability of the systems and its procedures to maintain the appropriate level of chemical and microbial control, taking seasonal variations into account, is demonstrated and documented.

(vi). Alert and action limits should be established for bacterial endotoxins and microbial load. These limits should meet any appropriate standard or appropriate legislation

(vii) WFI storage tanks are equipped with hydrophobic bacterial-retentive vent filters.

(viii) Sanitization or regeneration of water systems is carried out according to a predetermined schedule and also whenever established microbial counts are exceeded within any of the system's components. Consideration is given to controlling biofilm formation.

(ix). The WFI system is maintained at an elevated temperature and kept in continuous movement. Water velocity through pipes is sufficient to prevent microbial attachment.

(x) Piping is sloped to provide for complete drainage of the system. The system is free of dead legs.

(xi)All metal surfaces in contact with WFI should be, as a minimum, 316 stainless steel, and should be passivated upon or prior to installation and after changes.

(xii)While in use during processing, WFI is sampled daily from at least two points on a rotating basis so as to cover all outlets.

(xiii)Revalidation of water systems is required if any of the following situations arise:

(xiv) Unscheduled or extensive maintenance is performed on the system;

(xv) New or revised sections or components are added to or removed from the system; and

(xvi) The system exhibits an out-of-control trend in either chemical or microbiological parameters.

(xvii) The extent of the re-validation work necessary is determined jointly by the personnel from the quality control, engineering, production, and any other appropriate departments. A pre-approved protocol is signed and dated by the parties involved.

20.1.7 Personnel

(i)The personnel responsible for the manufacture and testing of sterile products have had training in microbiology.

(ii) High standards of personal hygiene and cleanliness are maintained. Personnel involved in the manufacture of sterile preparations are instructed to report any condition that may cause the shedding of abnormal numbers or types of contaminants. Periodic health checks for such conditions are conducted, and appropriate action (e.g., deciding whether to allow an individual to be involved in a particular operation) is taken by designated qualified personnel when necessary.

(iii) All personnel (including those whose duties involve cleaning and maintenance) employed in such areas receive regular training in disciplines relevant to the correct manufacture of sterile products, including reference to hygiene and to the basic elements of microbiology. When outside personnel who have not received such training (e.g., building or maintenance contractors) need to be brought in, particular care is taken with regard to their supervision.

(iv) Personnel 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 do not enter areas where sterile products are manufactured unless rigorous and clearly defined decontamination procedures have been followed.

(v). Only the minimum number of personnel required are present in areas where sterile products are manufactured; this is particularly important during aseptic processes. Inspections and controls are conducted from outside such areas to the extent that such an approach is possible.

(vi). Outdoor clothing is not brought into these areas. Personnel entering the changing rooms are already clad in standard protective garments designed for factory facilities. Changing and washing follow written procedures.

(vii). The clothing worn by personnel and its quality are adapted to the particular process and workplace, and the clothing is worn in such a way as to protect the product from contamination.

(viii). Clothing is appropriate to the environmental grade of the area where the personnel will be working. Written gowning procedures must be established for each environmental grade. Personnel must be trained according to these procedures prior to entry. Such training must be documented. Descriptions of the clothing required for each grade are given below.

For Grades A and B areas:

Gowns are sterilized and cover the skin and hair; headgear totally encloses the person's hair, as well as any beard or mustache, the headgear is tucked into the neck of the suit; a face mask is worn to prevent the shedding of droplets; sterilized protective goggles are worn; sterilized non-powdered rubber or plastic gloves and sterilized or disinfected footwear are worn; trouser-bottoms are tucked inside the footwear and garment sleeves are tucked into the gloves. The protective clothing sheds virtually no fibres or particulate matter and retains particles shed by the body.

For Grade C areas:

The person's hair, as well as any beard or mustache, is covered. A one- or two-piece trouser suit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes are worn. The protective clothing sheds virtually no fibres or particulate matter.

For Grade D areas:

The person's hair, as well as any beard or mustache, is covered. Protective clothing and appropriate shoes or overshoes are worn.

(ix) For every worker in an aseptic (Grades A and B) area, clean sterilized protective garments are provided at each re-entry. Gloves are regularly disinfected during operations. Masks and gloves are changed prior to every new working session.

(x). Clothing used in clean and aseptic areas is laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. Separate laundry facilities for such clothing are desirable. If fibres are damaged by inappropriate cleaning or sterilization, there may be an increased risk of shedding particles. Washing and sterilization operations follow standard operating procedures. Repair of clothing is carried out using appropriate materials (e.g., non-shedding thread).

(xi) Behavioural techniques aimed at maintaining sterility should be employed by personnel working in aseptic areas. These include:

(a) moving slowly and deliberately;

(b) keeping the entire body out of the path of unidirectional airflow;

(c) approaching any manipulation in a manner that does not compromise sterility of the product; and

(d) maintaining proper gown control.

20.1.8 Sanitation

(i)Walls, floors, ceilings, and equipment in clean areas are cleaned and, when required, disinfected in accordance with a written procedure. This procedure differentiates between procedures that are followed daily and those that are undertaken whenever fabrication of a different drug is about to begin.

(ii) Disinfectants and cleaning agents to be used in aseptic processing areas should be sterile.

(iii) A disinfectant program should also include a sporicidal agent since many common disinfectants are ineffective against spores.

(iv) Disinfectants and cleaning agents are monitored for microbial contamination and are sterile when used in Grades A or Grade B areas. Dilutions are kept in previously cleaned and sterilized containers and are not stored for long periods unless sterilized. Partly emptied containers are not topped up.

(v) Fumigation of clean and aseptic areas may be useful for reducing microbiological contamination in inaccessible places.

(vi) The cleaning procedures are validated, and the disinfection procedures are monitored.

(vii)The suitability, efficacy and limitations of disinfecting agents and procedures should be assessed including their ability to adequately remove potential contaminants from surfaces.

20.1.9 Manufacturing Control

(i) During all processing stages, precautions are taken to minimize contamination.

(ii) Preparations containing live microorganisms are neither made nor transferred into containers in areas used for the processing of other pharmaceutical products. Preparations containing only dead organisms or bacterial extracts may be dispensed into containers, in the same premises as other sterile pharmaceutical products, provided that validated inactivation procedures and validated cleaning procedures are followed.

(iii) Activities in these areas are kept to a minimum, especially when aseptic operations are performed. The movement of personnel is controlled and methodical in order to avoid excessive shedding of particles and organisms. The ambient temperature and humidity are controlled and monitored to ensure the comfort of personnel.

(iv) Prior to sterilization, possibilities for microbiological contamination of raw materials and packaging materials are kept to a minimum. Specifications include requirements for microbiological quality when monitoring has indicated the need for such requirements.

(v) Articles are sterilized and passed into the aseptic areas by the use of doubled-ended sterilizers equipped with interlocking doors or by another validated method.

(vi) Written standards are available specifying the air quality, including viable and non viable counts, to be maintained in clean and aseptic areas. Viable and non viable counts are taken at least once per shift in aseptic areas, while aseptic filling and aseptic manufacturing operations are carried out, and at appropriate intervals in areas where other manufacturing takes place.

(vii) Air monitoring of "critical areas", Grade A environments should normally yield no microbiological contaminants. Contamination in a critical area should be investigated and corrective actions implemented.

(viii) In Grade A and B areas, regular monitoring for particulate and viables should be performed during setup and all production operations. Low values for contaminants are reliable only when a large number of air samples are taken. Adequate data is available to generate confidence that the required conditions are met throughout the duration of the operations. Where justified, cascade sampling strategies for active air and particulates (e.g., sampling continuously through a rotation of sampling sites) may be acceptable. Settle plates should always be present in the critical zone. The total sample volume should not be less than 1 cubic meter per sample for Grades A and B areas and preferably also in Grade C. For Grade C areas, monitoring frequency is justified based on the criticality of the operations and historical data for the specified area. Where product is exposed in a Grade C area, monitoring should be conducted at least once per week. Sampling locations should be based on a formal risk analysis study considering historical results and those obtained during the classification of rooms.

(ix)Personnel working in aseptic processing areas should be microbiologically monitored once per shift. Typical monitoring sites should include operator's gloves and one gown site. Manual aseptic production processes require more aggressive personnel monitoring than automated aseptic production processes.

(x) The presence of containers and materials liable to generate fibres is minimized in clean and aseptic areas.

(xi) Following cleaning and sterilization, components, bulk-product containers, and equipment are handled in such a way that they are not re-contaminated. The stage of processing of components, bulk-product containers, and equipment is properly identified.

(xii)The interval between cleaning and sterilization of components, bulk-product containers, and equipment, as well as between their sterilization and use, is as short as possible and subject to a time-limit appropriate to the validated storage conditions.

(xiii)The time between the start of the preparation of a solution and its sterilization or filtration through a bacteria-retentive filter is as short as possible. A maximum permissible time is validated for each product, taking into account its composition and the prescribed method of storage.

(xiv) Water used in the preparation of parenterals is tested for endotoxins and complies with its approved specifications.

(xv) Water used for the final rinsing of container components that are used for parenteral drugs is tested for endotoxins unless such components are depyrogenated subsequently.

(xvi) Compressed air and gases that come in direct contact with the product/container primary surfaces must be of appropriate chemical, particulate and microbiological purity, free from oil, and must be filtered through a sterilizing filter at the point of use.

(xvii) The microbial contamination of products (bioburden) is minimal prior to sterilization. The maximum acceptable bioburden is established on a product by product basis, and should be founded on adequate product/process design and control. Acceptable bioburden levels are further demonstrated through the execution of validation studies. This limit is related to the efficiency of the method to be used and to the risk of pyrogens and bacterial endotoxins, which are not removed by sterilization. The bioburden should be monitored before sterilization. All solutions, particularly large-volume parenterals, are passed through a bacteria-retentive filter; if possible, this filtering occurs immediately before the filling process. Where aqueous solutions are held in sealed vessels, any pressure-release outlets are protected (e.g., by hydrophobic microbial air filters).

(xviii)Water, gas, or any heating or cooling fluid in contact with filled drug product containers (e.g., for the cool down cycle of sterilization loads) should present a low risk of microbial contamination.

(xix)Documented evidence that establishes the validation and validity of each sterilization process is available. The validation and validity of the sterilization process are verified at scheduled intervals, at least annually, and also whenever significant modifications or changes are made to the equipment. Loading patterns for all sterilization processes are established and validated.

20.2.0 Sterilization by heat

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

(i) Sufficient time is allowed for the whole load to reach the required temperature before measurement of the sterilizing time-period begins. This time is determined for each type of load to be processed.

(ii) After the high-temperature phase of a heat sterilization cycle, precautions are taken to prevent contamination of a sterilized load during cooling.

20.2.1 Sterilization by moist heat

(i) Both temperature and pressure controls are used to monitor the process. Control instrumentation is independent from both monitoring instrumentation and recording charts. Where automated controls and monitoring systems are used for these applications, they are fully validated to ensure that the critical process requirements are met. System and cycle faults are registered by the system and observed by the operator. The reading of the independent temperature indicator is periodically monitored. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position throughout the sterilization period. There are frequent leak tests on the chamber when a vacuum phase is part of the cycle.

(ii) The items to be sterilized, other than products in sealed containers, are wrapped, if necessary, in a material that allows the removal of air and the penetration of steam but that prevents re-contamination after sterilization. All parts of the load are in contact with the sterilizing agent at the required temperature and pressure for the required time.

(iii) Clean steam is used for sterilization and does not contain additives at a level that could cause contamination of product or equipment.

20.2.2 Sterilization by dry heat

(i) The process used includes air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted passes through a HEPA filter.

20.2.3 Sterilization by radiation

(i) The radiation dose is measured during the sterilization procedure. For this purpose, dosimetry indicators that are independent of dose rate are to be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters are inserted into the load in sufficient number and close enough together to ensure that there is always a dosimeter in the irradiator. Where plastic dosimeters are used, they are within the time limit of their calibration. Dosimeter absorbencies are read within a specified time period after exposure to radiation.

(ii) Biological indicators may be used as an additional control.

(iii)Materials handling procedures are designed so as to prevent mix-up between irradiated and non-irradiated materials. Radiation-sensitive colour disks are used on each package to differentiate between packages that have been subjected to irradiation and those that have not.

(iv) The total radiation dose is administered within a predetermined time span.

20.2.4 Sterilization with Ethylene Oxide

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

(ii) Before exposure to gas, materials are brought into equilibrium with the humidity and temperature required by the process. The time required for this is balanced against the opposing need to minimize the time before sterilization.

(iii)Each sterilization cycle is monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained is part of the batch record.

(iv)For each sterilization cycle, records are made of the time taken to complete the cycle, the pressure, the temperature and the humidity within the chamber during the process, the gas concentration, and total amount of gas used. The pressure and temperature are recorded throughout the cycle on a chart. The readings are part of the batch record.

(v)After sterilization, the load is stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process is validated.

(vi) Biological indicators are considered only as an additional method for monitoring the sterilization, except in the case of ethylene oxide sterilization, where they are a normal part of the monitoring criteria. If they are used, strict precautions are taken to avoid transferring microbial contamination from them.

(vii)Records are available indicating that the requirements for each sterilization cycle have been met. These records include all recording charts (e.g., time/temperature).

(viii)A clear visual means is used for differentiating products that have not been sterilized from those that have been sterilized. Each basket, tray, or other carrier of products or components should be clearly labeled with the name of the material, its batch number, and an indication of whether or not it has been sterilized. Such indicators as autoclave tape or radiation sensitive colour disks may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilization process. These visual means are not intended to give an indication that the lot is sterile.

20.2.5 **Aseptic Filling Operations**

A written standard designed to test the efficiency of the overall aseptic filling operation is maintained. This standard includes a requirement to perform normal aseptic filling operations using sterile media.

(i) The use of nutrient media that support microbial growth in trials to simulate aseptic operations (i.e., sterile media fills, "broth fills") is a valuable part of the overall validation of an aseptic process. Such trials have the following characteristics:

(ii) The trials simulate actual operations as closely as possible and also take into consideration worst case conditions;

(iii) The medium or media selected are capable of growing a wide spectrum of microorganisms, including those that would be expected to be found in the filling environment. Each batch of media used for process simulation must be tested for its growth promotion capabilities; and

(iv) The trials 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.

(v)The number of containers used for a media fill should be sufficient to allow a valid evaluation. If batches smaller than 5,000 units are filled, the minimum number of containers used for process simulation with sterile nutrient media should be equal to the maximum commercial batch size. The target is zero positives. Any positive unit indicates a potential problem regardless of the run size. All positives should be identified, and should result in a thorough, documented investigation and any identified corrective action implemented.

Recommended criteria for assessing state of aseptic line control are as follows:

(i) When filling fewer than 5000 units, no contaminated units should be detected. One (1) contaminated unit is considered cause for re-validation, following an investigation.

(ii) When filling from 5,000 to 10,000 units, one (1) contaminated unit should result in an investigation, including consideration of a repeat media fill. Two (2) contaminated units are considered cause for re-validation, following investigation.

(iii) When filling more than 10,000 units, one (1) contaminated unit should result in an investigation. Two (2) contaminated units are considered cause for re-validation, following investigation.

(iv) Investigations of gross media fill failures should include an assessment of the potential impact on sterility assurance of batches filled since the last successful media fill.

(vi)A matrix approach to process simulation may be developed for each filling line, and should include elements such as the type of products filled, size of lots, container and closure configuration, fill volume, line speed, filling line configuration and components, and sterile hold times.

(vii) A process simulation run should be performed of sufficient duration to cover all routine manipulations and operations, various interventions known to occur during normal production, as well as worst case situations.

(viii) The process simulation test should simulate all the specific manufacturing steps, such as product transfer, sterile filtration, filling, transfer of semi-stoppered vials to the lyophilizer, the lyophilization process, and stoppering and crimping of vials.

(ix) The process simulation test program incorporates a representative number, type, and complexity of normal interventions that occur with each run, as well as non-routine interventions, and events (e.g., maintenance, stoppages, equipment, adjustments). A pre-defined list of all permitted interventions should be documented and incorporated into process simulation on a periodic basis.

(x) The fill volume should be sufficient to assess potential microbial contamination, and to ensure the complete contact with all sterile surfaces inside the container when the container is inverted and swirled. Consideration should be given to incubation of filled vials with media contacting the closure system (e.g., inverted storage).

(xi)Incubation conditions should be suitable for recovery of bioburden and environmental isolates. Following the aseptic processing of the medium, the filled containers are incubated at 22.5 °C ± 2.5 °C or at 32.5 °C ± 2.5 °C. All media filled containers should be incubated for a minimum of 14 consecutive days. If two temperatures are used for incubation of media filled samples, then these filled containers should be incubated for at least 7 consecutive days at each temperature starting with the lower temperature.

(Xii) Initial validation or re-validation requires three successful process simulation tests. In the absence of observed issues with respect to environmental monitoring or sterility testing, re-validation should take place at least semi-annually with a minimum of a single process simulation. Whenever a significant alteration in the product, premises, equipment, or process occurs or failure of process simulation occurs, re-validation is required.

(xiii) Every person who is normally allowed to be in the filling room during aseptic filling operations must participate in the process simulation test, during which they must perform their normal assigned duties. Only trained and qualified personnel who have successfully participated in a process simulation test should be permitted to participate in aseptic processing. Records should be maintained.

(xiv)For aseptically filled vials, the filling/stoppering must be performed under Grade A conditions with a Grade B background. Because complete integrity may not yet be achieved at this point, if crimping does not take place in the aseptic core, stoppered vials should be protected with a Grade A air supply within a minimum of a Grade D environment until the cap has been crimped. The following must also be considered:

(xv) the crimping should be done as soon as possible after the stoppering;

(xvi) the distance between the exit of the Grade A/B to the actual point of crimping in the lower environment should be kept as short as possible;

(xvii) procedures are in place to ensure that the stoppers are properly seated prior to the crimping operation;

(xviii) line stoppages and time lapses are documented; and

(xviii)stoppered vials which do not get crimped within the established time lapse are segregated and disposed of in accordance with standard operating procedures (SOPs).

20.2.6 Sterilization by Filtration

(i)The sterilizing filtration should be validated to reproducibly remove viable microorganisms from the process stream, producing a sterile effluent. Validation studies should consider factors that can affect filter performance, which generally include viscosity and surface tension of the solution to be filtered, pH, compatibility of the material or formulation components with the filter, pressures, flow rates, batch volume, maximum use time, temperature, osmolality, and the effects of hydraulic shock.

(ii)The microorganism *Brevundimonas diminuta* (ATCC 19146) when properly harvested, grown and used, is a common challenge microorganism for sterilizing filters because of its size (0.3 µm mean diameter). A challenge concentration of at least 10^7 organisms per cm^2 of effective filtration area should generally be used, and should result in no passage of the challenge microorganism. Direct inoculation into the drug formulation is the preferred method because it provides an assessment of the effect of the drug product on the filter matrix and on the challenge organism (except for products with inherent bactericidal activity against this microbe, or oil-based formulations).

(iii) Use of secondary sterilizing filters should be considered. This second filtration via a further sterilized micro-organism retaining filter, immediately prior to filling, should be carried out as close as possible to the filling point.

(iv) When the use of one sterilizing filter has been validated to achieve sterilization of a specific product, then the sterilizing filter must satisfactorily pass integrity testing before and after use.

(v)When more than one sterilizing filters are used in the filter train, all filters must be tested before use. The secondary sterilizing filter does not require post-use integrity testing unless the primary sterilizing filter fails. In that case, the secondary sterilizing filter must satisfactorily pass integrity testing before and after use. If there are documented reasons for not being able to perform pre-filtration filter integrity testing of either filter in a series after sterilization, (e.g., if sterility downstream of the first filter may be compromised), the filters should be tested both prior to sterilization and after use.

20.2.7. Blow/fill/ seal

i) Blow/ fill/ seal equipment used for aseptic production is fitted with an effective Grade A air shower and operated in at least a Grade C background environment. The background environment should comply with the viable and non viable limits at rest and viable limit when in operation.

(ii) Blow/ fill/ seal equipment used for the production of products that are terminally sterilized should be installed in at least a Grade D background environment.

20.2.8 Isolator technology

i) The environmental cleanliness within an isolator is a Grade A located in at least a Grade D background environment.

(ii) Decontamination procedures should ensure full exposure of all isolator surfaces to the chemical agent. Decontamination methods that render the inner surfaces of barrier and isolator systems free of viable microorganisms should be developed and validated. Residues from the decontamination process should not negatively impact product or primary contact surfaces.

(iii) For sterilization of the filling line, where decontamination methods are used to render certain product contact surfaces free of viable organisms, a minimum of a six-log reduction should be demonstrated using a suitable biological indicator.

iv) When using Aseptic processing in isolators the integrity and seams of gloves and half suits should receive daily attention when in use and be addressed by a comprehensive preventative maintenance program. Replacement frequencies should be established in written standard operating procedures that will ensure that parts will be changed before they breakdown or degrade. Transfer systems, gaskets, and seals should be covered by a written maintenance program.

(v) Protection against potential ingress of any airborne particles from the environment surrounding the isolator must be a design feature. A breach of isolator integrity should normally lead to a decontamination cycle. Integrity can be affected by power failures, valve failure, inadequate overpressure, holes in gloves and seams, or other leaks.

(vi) Air quality within the isolator should be monitored for microbiological quality and particulates during each shift.

20.2.9 Quality Control

(i)Filled containers of parenteral products are inspected individually for the presence of particulates and other defects. When inspection is done visually, it takes place under suitable and controlled conditions of illumination, and background, and line speed. Operators doing the inspection pass regular eyesight checks, while wearing corrective lenses if such lenses are normally worn, and are allowed frequent breaks from inspection. Operators are subjected to routine checks for their efficiency in detecting defective units. Where other methods of

inspection are used, the process is validated and the performance of the equipment is checked at intervals.

(ii). Filled ampoules are subjected to a leaker test (e.g., dye immersion test). Samples of other containers closed by appropriately validated methods are checked for integrity of seal and/or maintenance of vacuum where applicable after an appropriate predetermined period.

(iii). Samples taken for sterility testing are representative of the whole of the batch, but in particular include samples taken from parts of the batch considered to be most at risk of contamination, for example:

(iv) For products that have been filled aseptically, samples include the first and last containers filled, and those filled after any significant interruption.

(v) For products that have been heat-sterilized in their final containers, consideration is given to taking samples from the potentially coolest part of the load. Each sterilizer load is treated as a separate batch for sterility testing purposes.

(vi)The validated sterility test applied to the finished product is only one measure taken to assure sterility. It is to be interpreted in conjunction with the environmental and batch processing records.

(vii) Batches failing an initial sterility test are rejected unless a thorough investigation is carried out and the initial test is invalidated.

(viii). Biological indicators used for routine monitoring of a sterilization process and when used in validation/ re-validation studies should be tested to verify the accuracy of the population count stated by the vendor.

(ix). Media used for environmental monitoring should be tested for its growth promotion capability, in accordance with a formal written program.

(x) Microbial quantification must be based on scientifically sound methods. Because devices (e.g., air sampler) vary, the user should assess the suitability of their selected monitoring devices before they are placed into service. Such devices should be calibrated and used according to appropriate procedures.

(xi)Environmental monitoring data generated in Grade A areas should be reviewed as part of product batch release. A written plan should be available that describes the actions to be taken when an environmental monitoring occurs.

APPENDIX A: ACRONYMS AND GLOSSARY OF TERMS

Acronyms

1. **API:** Active Pharmaceutical Ingredient
2. **CoC:** Certificate of Compliance
3. **DIN:** Drug Identification Number
4. **GMP:** **Good manufacturing practice**
5. **ICH:** International Conference on Harmonisation
6. **OOS:** Out of specification
7. **SOP:** Standard Operating Procedure
8. **WFI:** Water for Injection
9. **WHO:** World Health Organization

Glossary of Terms

1. **Active Pharmaceutical Ingredient :**

Any substance or mixture of substances that is intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

2. **Airlock :**

An enclosed space with two or more doors, that is interposed between two or more rooms, usually of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when either people or goods need to enter or leave them.

3. **Aseptic Area :**

A zone or zones within a clean area where Grade A or B conditions are maintained.

4. **Aseptic Process :**

A method of producing a sterile product in which sterile bulk drug or sterile raw materials are compounded and assembled with sterile packaging components under Grade A or B conditions .

5. Batch :

A quantity of drug in dosage form, a raw material, or a packaging material, homogeneous within specified limits, produced according to a single production order and as attested by the signatories to the order. In the case of continuous manufacture, a batch corresponds to a defined fraction of the production, that is characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

6. Batch Certificate :

A certificate issued by the manufacturer of a lot or batch of a drug that is exported within the framework of a mutual recognition agreement and in which the manufacturer:

(a) identifies the master production document for the drug and certifies that the lot or batch has been manufactured, packaged/labeled and tested in accordance with the procedures described in that document;
(b) provides a detailed description of the drug, including

- a statement of all properties and qualities of the drug, including the identity, potency and purity of the drug, and
- a statement of tolerances for the properties and qualities of the drug;

(c)identifies the analytical methods used in testing the lot or batch and provides details of the analytical results obtained;

(d)sets out the addresses of the buildings at which the lot or batch was

manufactured, packaged/labeled and tested; and

(e)certifies that the lot or batch was fabricated, packaged/labeled and tested in accordance with the good manufacturing practices of the regulatory authority that has recognized those buildings as meeting its good manufacturing practices standard.

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7. Batch Number*:*

A distinctive combination of numbers and/or letters that specifically identifies a batch. The batch number appears on the batch records, certificates of analysis, etc.

8. Bio-burden :

The total number of micro-organisms associated with a specific item prior to sterilization**.**

9. Bracketing:

The design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, package size) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different sized capsule shells). Bracketing can be applied to different container sizes or to different fills in the same container closure system.

10. Bulk Drug :

A drug in dosage form that is not in its final packaging, usually in quantities larger than the largest commercially available package size.

11. Bulk Process Intermediate :

Any intermediate form of a drug (e.g., final bulk intermediate, bulk material, bulk concentrate, drug substance) which must undergo further processing before it becomes a final product. They are usually characterized by a holding time, storage conditions and the application of in-process tests.

12. Campaign Production :

Sequential processing of material, either more than one product in a multi-product facility or more than one lot of the same product in a dedicated facility, over a defined period of time. Campaign production could occur at any point in a production process where common rooms/suites and/or equipment are reused for multiple products/lots.

13. Certificate of Analysis (COA) :

A document containing the name and address of the laboratory performing the test(s), name and specifications of the material(s), test(s) performed, test method(s) used, actual numerical results, approval date(s), signature of approver, and any other technical information deemed necessary for its proper use.

14. Certificate of Manufacture :

A document issued by a vendor to a distributor or importer that attests that a specific lot or batch of drug has been produced in accordance with its master production documents. Such certificates include a detailed summary of current batch documentation, with reference to respective dates of revision, manufacture, and packaging, and are signed and dated by the vendor's quality control

department. For drugs that are fabricated, packaged/labeled and tested in MRA countries, the batch certificate is considered to be equivalent.

15. Certificate of Pharmaceutical Product (CPP) :

A certificate issued by the Inspectorate establishing the regulatory status of the pharmaceutical, biological or veterinary product listed and the GMP status of the manufacturer of the product. This certificate is in the format recommended by the WHO.

16. Change Control :

A written procedure that describes the action to be taken if a change is proposed *(a)* to facilities, materials, equipment, and/or processes used in the manufacture, packaging, and testing of drugs, or *(b)* that may affect the operation of the quality or support system.

17. Changeover Procedure :

A logical series of validated steps that ensures the proper cleaning of suites and equipment before the processing of a different product begins.

18. Clean Area :

A room or suite of rooms where Grade C or D conditions are required. The rooms have a defined environmental control of particulate and microbial contamination and are constructed, maintained, and used in such a way as to minimize the introduction, generation, and retention of contaminants.

19. Commitment Batches:

"Production batches of a drug product for which the stability studies are initiated or completed post approval through a commitment made in the registration application.

20. Computerized Systems :

Consists of all components, including but not limited to hardware, software, personnel, and documentation, necessary to capture, process, transfer, store, display, and manage information.

21. Contractor :

Legal entity carrying out activities on behalf of a company pursuant to a written agreement. This includes other sites within the same corporate structure.

22. Critical Area :

Area in which the sterilized drug product, containers, and closures are exposed to environmental conditions that must be designed to maintain product sterility. Activities conducted in this area include manipulations, such as aseptic connections, sterile ingredient additions, filling and closing operations.

23. Critical Process :

A process that if not properly controlled may cause significant variation in the quality of the finished product.

24. Dosage Form :

A drug product that has been processed to the point where it is now in a form in which it may be administered in individual doses.

25. Drug :

"Any substance or mixture of substances manufactured, sold, or represented for use in *(a)* the diagnosis, treatment, mitigation, or prevention of a disease, a disorder, an abnormal physical state, or the symptoms thereof, in humans or animals, *(b)* restoring, correcting, or modifying organic functions in humans or animals

26. Expiry Date :

"Means the earlier of *(a)* the date, expressed at minimum as a year and month, up to and including which a drug maintains its labeled potency, purity and physical characteristics, and *(b)* the date, expressed at minimum as a year and month, after which the manufacturer recommends that the drug not be used.

27. Finished Product :

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

28. Grade A Air Supply :

A supply of air which is HEPA filtered, and at the point of supply meets when tested, the non-viable particulate requirements of a Grade A area.

29. Growth Promotion :

A test in which prepared media is challenged with pre-selected organisms to assure that the media is capable of supporting growth.

30. In-process Control :

Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the finished product conforms to its specifications. The control of the production environment or equipment may also be regarded as a part of in-process control.

31. In-process Drug :

Any material or mixture of materials that must, to become a drug in dosage form, undergo further processing.

32. In-process Testing :

The examination or testing of any material or mixture of materials during the manufacturing process.

33. Lot :

A quantity of any drug in dosage form, a raw material, or a packaging material, homogeneous within specified limits, constituting all or part of a single batch and identified by a distinctive lot number that appears on the label of the finished product.

34. Manufacturing Batch Record :

Records demonstrating that the batch of a drug was manufactured in accordance with the approved master production documents.

35. Master Formula :

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

36. Master Production Documents :

Documents that includes specifications for raw material, for packaging material and for packaged dosage form; master formula (including composition and instructions as described in the definition above), sampling procedures, and critical processing related standard operating procedures (SOPs), whether or not these SOPs are specifically referenced in the master formula.

37. Matrixing :

"The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and possibly in some cases, different container closure systems.

38. Packaging Batch Record :

Records demonstrating that the batch of a drug was packaged in accordance with the approved master production documents.

39. Potency:

The activity or amount of active moiety, or any form thereof, indicated by label claim to be present.

40. Process Validation :

Establishing documented evidence with a high degree of assurance, that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. Process validation may take the form of Prospective, Concurrent or Retrospective Validation and Process Qualification or Re-validation.

41. Production :

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

42. Quality Risk Management :

A systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product.

43. Reconciliation :

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

44. Reprocessing :

Subjecting all or part of a batch or lot of an in-process drug, a bulk process intermediate (final biological bulk intermediate) or a bulk drug of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary and are validated and pre-approved by the quality control department or as part of the marketing authorization.

45. Re-test Date :

"The date when a material should be re-examined to ensure that it is still suitable for use.

46. Re-test Period :

"The period of time during which a drug substance can be considered to remain within the specifications and therefore acceptable for use in the fabrication of a given drug product, provided that it has been stored under defined conditions; after this period, the batch is re-tested for compliance with specifications and then used immediately.

47. Reworking :

"Subjecting an in-process drug, a bulk process intermediate (final biological bulk intermediate), or final product of a single batch/lot to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization." (WHO GMP)

48. Shelf Life :

The time interval during which a drug product is expected to remain within the approved specification provided that it is stored under the conditions defined on the label and in the proposed containers and closure.

49. Specifications :

"Means a detailed description of a drug, the raw material used in a drug, or the packaging material for a drug and includes:

(a) a statement of all properties and qualities of the drug, raw material or packaging material that are relevant to the manufacture, packaging, and use of the drug, including the identity, potency, and purity of the drug, raw material, or packaging material,

(b) a detailed description of the methods used for testing and examining the drug, raw material, or packaging material, and

(c) a statement of tolerances for the properties and qualities of the drug, raw material, or packaging material.

50. Standard Operating Procedure (SOP) :

A 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; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documents.

51. Sterile :

Free from viable microorganisms.

52. Terminal Sterilization :

Sterilizing a drug in its final closed container.

53. Validation :

The documented act of demonstrating that any procedure, process, and activity will consistently lead to the expected results. Includes the qualification of systems and equipment.

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