# ARAB Guidelines on
# Current Good Manufacturing Practice (cGMP) for
# Pharmaceutical Products

# 2007

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## Preamble

Great attention is required in the manufacturing of pharmaceutical products. This is not only because of the current large scale use of pharmaceutical preparations in health care but also because of the possible dangers resulting from their high potency as therapeutic agents and the complexity of their formulation technology.

Since quality assurance of drug products is the main responsibility of the pharmaceutical industry and the testing of finished products by itself is no longer appropriate or adequate to insure quality, intensive efforts should be made to put in use Good Manufacturing Practice GMP.

However, the implementation of GMP by all the Arab pharmaceutical manufacturers requires development of clear and appropriate guidelines that provide general principles and guidance on each aspect of the pharmaceutical industry . These shall be binding to the Arab pharmaceutical industry as well as foreign suppliers .

Need will call later for practical guidelines relating to the implementation of the GMP and aiming at providing specific guidance in a way that lead to develop further the present Arab pharmaceutical industry .

The implementation of these essential guidelines is the responsibility of the health authorities in each Arab country . Such guidelines should periodically be reviewed and , when necessary, revised by competent GMP Arab experts .

Besides improving the quality of pharmaceutical products in general , the implementation of such Arab GMP guidelines will significantly upgrade the performance of the pharmaceutical industry's manpower, improve the image of the Arab pharmaceutical industry and can serve as a model of accomplishment for other Arab industries . In addition, this will lead to wide international recognition and confidence .

Finally , the implementation of GMP by all the Arab pharmaceutical manufacturers shall foster self-reliance and self-actualization among those who are involved in the pharmaceutical industry and help in promoting harmonization of Arab Quality Assurance Scheme among Arab countries as well.

## Introduction to the Second Edition

Since 1991 when the first edition of the Arab good manufacturing practice guidelines was issued . Substantial changes have occurred in the concept of good manufacturing and in the broad concept of quality management , and many new editions of good manufacturing requirements for quality management have been issued by the international standardization organization ( As it appeared in the ISO 9000 ) .

All this made it necessary to revise the first edition of the Arab's GMP Guidelines so as to be in line with the different international requirements. A committee was formed that brought out this edition according to the following criteria :-

1- First edition of Arab GMP guidelines as the baseline of this work because it was the result of joint Arab effort .
2- WHO-GMP guidelines , which was published in the thirty third reports, as guidance especially to cover , in a brand aspect , the elements of quality management and system .

# DEFINITIONS

**Active ingredient**
A pharmacologically active substance in a pharmaceutical product.

**Air-lock**
An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing class of cleanliness, for the purpose of controlling the air-flow between those rooms when they need to be entered. An air-lock is designed for and used by either people or goods.

**Authorized person**
A person responsible for the release of batches of finished products for sale.

**Batch (or lot)**
A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity.

**Note:** It may be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

**Batch number (or lot number)**
A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificate of analysis, etc.

**Batch numbering system**
Standard Operating Procedure (SOP) describing the details of the batch numbering.

**Batch records**
Includes all documents associated with the processing and packaging of a batch of bulk product or finished product. They provide a history of each batch of product, and also of all other relevant circumstances pertinent for the quality of the final product.

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

**Calibration**
The set of operations which establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially including weighing), recording and control, or values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the measuring results should be established.

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

**Climatic Zones**
The concept of dividing the world into four zones based on defining the prevalent annual climatic conditions.

**Consignment ( Delivery)**
The quantity of starting material or of a drug product made by one manufacturer and supplied at one time in response to a particular request or order.

**Critical process**
A process which may cause variation in quality attributes.

**Cross-Contamination**
Contamination of starting material, intermediate product, or finished product with another starting material or product during production.

**Date of manufacture**
The date fixed for individual batch indicating the start date of the manufacture.

**Dosage Form**
Refers to the gross physical form in which a drug is administered to or used by a patient.

**Drug product (Pharmaceutical product)**
A dosage form containing one or more active therapeutic ingredients along with other substances included during the manufacturing process, or it is any substance or mixture of substances that is manufactured, sold, put for sale or presented for use in:

a) The treatment, mitigation, prevention or diagnosis of disease, an abnormal physical state or the symptoms thereof in man or animal.
b) The restoration, correction or modification of organic functions in man or animal.

**Expiration Dating Period ( Shelf-Life)**
The interval of time that a drug product is expected to remain within specifications as determined from stability studies on a limited number of batches of the product . the expiration dating period is used to establish the expiration date of individual batches.

**Expiration date**
The date fixed for each batch before which the batch still meets the required standard specifications for quality.

**Finished product**
A pharmaceutical product which has undergone all stages of manufacturing operations including packaging.

**Good Manufacturing Practice (GMP)**
The part of quality assurance aimed at ensuring that products are manufactured to a quality appropriate to their intended use.

**Good Pharmacy Practice:**
Is a means of providing service of appropriate quality to every patient. The mission of pharmacy practice is to provide medications and other health care products and services - and to help people and society to make the best use of them.

**Inactive Ingredient**
Any component other than active ingredient

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

**The International Organization for Standardization ( ISO)**
Is a worldwide federation of national standards bodies ( ISO Member Bodies). The work of preparing international standards is normally carried out through ISO technical committees.

**Intermediate product**
Partly processed material which must undergo further processing steps before it becomes a bulk product.

**Injectables**
**- Large-volume parenterals - LVP**
Any sterile solution intended for parenteral application with a volume of 100 ml or more in one container of the finished dosage form.
**- Small-volume parenterals - SVP**
Any sterile solution intended for parenteral application with a volume of less than 100 ml in one container of the finished dosage form.

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

**Manufacturer**
The company which carries out at least one step of manufacture.

**Marketing authorization**
A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling and shelf life.

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

**Master record**
A document or set of documents serving as a basis for the batch documentation (blank batch record).

**Overage**
The excess quantity of active ingredient that must be added to the preparation to maintain at least 90%of the labeled amount during the expected shelf-life of the product.

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

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

**Processing**
That part of production cycle starting from weighing and compounding of starting materials and ending into bulk product.

**Packaging**
All operations, including filling and labeling, which a bulk product has to undergo in order to become a finished product.

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

**Quality Assurance**
Quality Assurance is a global concept that is concerned with all matters which influence the quality of a product before, during and after its manufacture. It is defined as all those planned and systematic activities implemented within the quality system and demonstrated as needed to provide adequate confidence that medicinal products are of the quality required by their intended use.

**Quality control**
Quality control is that part of GMP concerned with sampling, specifications, and testing and with the organization, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has

been judged to be satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

**Quality Management**

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

**Quarantine**

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

**Reconciliation**

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

**Recovery (blending)**

The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture.

**Reprocessing**

The reworking of all or part of a batch of an unacceptable quality from a defined stage of production so that its quality may be rendered acceptable by one or more additional operations.

**Returned products**

Finished products sent back to the manufacturer.

**Specifications**

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

**Stability**

The ability of a pharmaceutical product, in a specific container closure system, to remain within the defined physical ,chemical , microbiological , therapeutic , and toxicological specifications till the end of the stated dating , under defined storage conditions.

**Stability Indicating Assay**

The assay which is sensitive and selective to determine quantitatively the active ingredient in the presence of its decomposition products and interfering exipients.

**Standard operating procedures (SOPs)**

A written authorized procedure which gives 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, etc.). Certain SOPs may be used to supplement a product-specific Master and Batch production documentation.

**Starting material**
Any substance of a defined quality used in the production of a drug product, but excluding packaging materials. A starting material is sometimes known as raw material or an ingredient, although not all starting materials remain as ingredients of the final product.

**Status**
The classification of any goods, materials, containers or machines in relation to their acceptance (or otherwise) for use, further processing or distribution (e.g. 'Quarantine', 'On Test', 'Released', 'Restricted Use', 'Rejected', 'Clean', 'To be Cleaned',).

**Storage**
The term used to describe the safe keeping of starting materials , packaging materials , components received , semifinished ,inprocess , and finished products awaiting dispatch . The term also applied for safe keeping of materials and products in drug stores, pharmacies , hospitals –etc., under the specified conditions.

**Stress testing ( Accelerated Testing)**
Studies designed to increase the rate of chemical or physical degradation of a pharmaceutical substance or pharmaceutical product by using exaggerated storage conditions . The purpose is to determine kinetic parameters, if possible, and /or to predict the tentative expiration dating period.

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

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

# 1. QUALITY

## 1.1 Quality Management

### Concept and objective

Quality management is that aspect of management function that determines and implements the "Quality Policy". Quality policy is the overall intentions and directions of an organization regarding quality, as formally expressed by top management.

Quality management includes strategic planning, allocation of resources and other systemic activities for quality, such as quality planning, operations and evaluations.

The attainment of desired quality requires the commitment and participation of all members of the organization whereas the responsibility for quality management belongs to top management.

The quality system of an organization is influenced by the objectives of the organization, by the product or service and by the practices specific to the organization, and therefore the quality system varies from one organization to another.

In the pharmaceutical industry, product must be fit for intended use and complying with the marketing authorization, thus presenting no risk to patient's life. The attainment of quality objectives is the primary responsibility of senior management. However, the actual quality of the product presented to the patient is the responsibility of everybody concerned with all stages of manufacture, control, and distribution. To achieve quality objectives reliably, there must be a comprehensively designed and correctly implemented system of quality.

The basic concepts of quality assurance, GMP, and quality control (as defined in this guide) are interrelated aspects of quality management, and they embrace all the necessary elements of a quality system including organizational structure, responsibilities, procedures, processes, and resources.

## 1.2 Quality Assurance

### 1.2.1 Principle

Quality Assurance is a global concept that is concerned with all matters which influence the quality of a product before, during and after its manufacture. It is defined as all those planned and systematic activities implemented within the quality system and demonstrated as needed to provide adequate confidence that medicinal products are of the quality required by their intended use. Quality Assurance therefore, incorporates Good Manufacturing Practice plus other factors outside the scope of this guide (such as original product design and development).It is the responsibility of senior management to establish systems for ensuring the required quality. It requires the commitment and cooperative spirit by staff in different departments and at all levels within the company.

**1.2.2** Quality assurance can only be achieved if the following conditions have been applied:

**a)** The entire processes of production and control procedures are clearly defined in writing and well communicated to all concerned people.
**b)** The required conditions for the manufacture, supply, and use of the correct starting and packaging materials are provided.
**c)** Providing the required resources of competent personnel, suitable and sufficient premises, equipment, and facilities.
**d)** Responsibilities and quality functions of all concerned people at different management levels are clearly defined in a written job description form.
**e)** Authorized person(s) have to certify each production batch before its distribution to ensure that it has been produced and controlled according to marketing authorization and any other regulations relevant to the production, control and release of medicinal products.
**f)** Proper storage, distribution and handling of the product so that its quality is maintained throughout its shelf life.
**g)** Setting procedure for self-inspection and/or quality audit which regularly appraises the effectiveness and applicability of the quality assurance system.

## 1.3 Good Manufacturing Practice (GMP)

**1.3.1** **GMP** is that part of Quality Assurance aimed at ensuring that products are consistently manufactured to the quality appropriate to their intended use and as required by marketing authorization. It is thus concerned with both production and quality control.

**1.3.2** **The essential parts of GMP are**:

**a)** All manufacturing processes are clearly defined and known to be capable of consistently achieving the desired results by conducting necessary validation studies.
**b)** All necessary facilities are provided including:
- Appropriately 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.

**c)** Procedures are written in instructional form, in clear and unambiguous manner and specifically applicable to the facilities provided.
**d)** Records are made during manufacturing which should demonstrate that all steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any deviations are fully recorded and investigated.
**e)** Records of manufacture and distribution which enable the complete history of a batch to be traced are retained in comprehensible and accessible form.
**f)** A suitable system for dealing with complaints should be available.
**g)** a suitable batch recall system should be available for removing any batch from sale or supply if deemed necessary.

## 1.4 Quality Control

**1.4.1** Quality control is that part of GMP concerned with sampling, specifications, and testing and with the organization, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

**1.4.2** Each holder of a manufacturing authorization should have a quality control department. The independence of quality control from production and other departments is considered fundamental to the satisfactory operation of quality control. This department is under the authority of a person with appropriate qualifications and experience.

**1.4.3** The Quality Control duties pertain (not exclusive) to establishing, validating and implementing all quality control procedures, evaluating, maintaining and storing the reference standards of substances, ensuring the correct labeling of containers of materials and products, ensuring the monitoring of the stability of the active pharmaceutical substances and the products, participating in the investigation of complaints related to the quality of the product,-----etc.

**1.4.4** The Quality Control is responsible for and authorized to approve and reject starting materials, packaging materials and drug products, and to review production records to assure that no errors have occurred, or if errors have occurred, they have been fully investigated.

# 2. PERSONNEL

## 2.1 Principle

A satisfactory system of quality assurance, and the manufacture of a product with the quality appropriate for its intended use rely to a great extent on personnel who are involved in performing all the tasks for which the manufacturer is responsible. For this reason, there must be sufficient qualified personnel who are experienced trained to carry out their responsibilities.

**2.2** The manufacturer should have an updated organization chart. Personnel duties and responsibilities should be clearly explained to them and recorded as written job descriptions or by other suitable means.

**2.3** All personnel should receive necessary training in areas relevant to their work and to hygienic aspects. They should be aware of the principles of GMP that affect them.

**2.4** Key personnel include the head of production, quality control and the authorized person(s). They shall have a back-ground of appropriate qualifications, education and experience to ensure proper judgment that at all times products are manufactured with quality required by their intended use.

**2.5** The heads of production and quality control should be independent of each other. They shall be responsible for supervising the manufacture and control procedures and those people who carry out these procedures. They can delegate some of their functions to other staff if necessary, however, the responsibility cannot be delegated.

## 2.6 Key personnel responsibilities

**2.6.1** The head of production department has generally the following responsibilities:

**a)** to ensure that products are manufactured and stored according to the appropriate documentation in order to obtain the required quality;

**b)** to ensure that the necessary training of production personnel is carried out and adapted according to need;

**c)** to approve the instructions relating to production operations and to ensure their strict implementation;

**d)** to ensure that the production records are evaluated and signed by a designated person before they are transmitted to the Quality Control department.

**e)** To check the maintenance of his department, premises, and equipment;

**f)** to ensure that the appropriate validation and calibration of control equipment is performed and recorded.

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

**a)** to approve specifications, sampling instructions, test methods, and other quality control procedures ;

**b)** to ensure that all necessary testing is carried out;

**c)** to approve or reject, as he sees fit, starting materials, packaging materials, and intermediate, bulk and finished products;

**d)** to evaluate batch records.

**e)** to approve and monitor analyses carried out under contract;

**f)** to check the maintenance of the department, premises and equipment;

**g)** to ensure that appropriate validations, including those of analytical procedures, and calibration of control equipment are done;

**h)** to ensure that the necessary training of quality control personnel is carried out and adapted according to need.

**2.6.3** The heads of production and quality control departments generally have some shared responsibilities relating to quality. These may include monitoring and control of manufacturing environment, plant hygiene, process capability studies, training of personnel, approval of suppliers of materials and of contract acceptors, protection of products and materials against spoilage and deterioration, and retention of records. It is important that both direct and shared responsibilities are understood by those concerned.

## 2.7 Training

All production and quality control personnel should be trained in the principles of GMP and in the practice and the relevant theory of the tasks assigned to them. Similarly, all other personnel (e.g. maintenance, service, cleaning) whose duties take them into manufacturing areas, or which bear upon manufacturing activities, should receive appropriate training.

**2.7.1** Training should be in accordance with written programs approved by the production manager and as appropriate by quality manger.

**2.7.2** A special attention should be given to training of operators working in aseptic or clean areas, or with highly potent materials.

**2.7.3** Training should be given at recruitment and be augmented and revised as necessary.

**2.7.4** Periodic assessments of the effectiveness of training programs should be made and checks should be carried out to confirm that designated procedures are being followed by staff at all levels.

## 2.8 Health of personnel

There shall be a suitable health program for medical checks for personnel before and during their employment. The type of medical check shall depend on the nature of work done by the employee.

# 3. PREMISES

**3.1 Principle**

Premises should be located, designed, constructed, and equipped in a manner suitable for the purpose of drug product manufacturing. The individual working areas should be adequate so that any risk of confusion, cross-contamination or other mistakes are reduced to a minimum.

**3.2** Premises should be sighted to avoid contamination from external environment or adjacent premises.

**3.3** Animal houses should be well isolated from manufacturing areas.

**3.4** Premises should be constructed and maintained with the object of protection against weather, ground seepage at the entrance and preventing the entry of animals and insects.

**3.5** All premises including production areas, laboratories, store, passage ways and external surroundings should be maintained in a clean and tidy conditions.

**3.6** Protection from the weather should be provided for receiving and dispatch areas, and for materials and products in transit.

**3.7** Premises should provide sufficient space to allow orderly and logical placement of equipment and materials such that to avoid cross-contamination between drugs or substances and minimize the risk of omission of any manufacturing step.

**3.8** Floors in processing areas should be made of impervious materials, laid to an even surface. They should be free from cracks and open joints, and should allow prompt and efficient removal of any spillage. Walls should be sound and finished with a smooth impervious and washable surface. Ceilings should be constructed and finished that they can be maintained in a clean condition. The coving of junctions between walls, floors and ceilings in critical areas is recommended.

**3.9** Maintenance of premises is a must. The condition of building should be examined regularly and repairs are to be made where necessary. Attention should be paid to ensure that building repair or maintenance operations do not spoil products.

**3.10** Lighting, ventilation and, if necessary, air conditioning are required to maintain a satisfactory environmental conditions that will not adversely affect the drug products during manufacture and/or storage.

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

**3.12** Changing rooms should be separate from, or partitioned from processing areas. Toilets should be well ventilated and do not directly communicate with production or storage areas.

**3.13** Storage areas should provide adequate space, and should be arranged and equipped to allow dry, clean and orderly placement of stored materials and products, wherever necessary, under controlled conditions of temperature and humidity.

**3.14** There should be suitable and effective separation of quarantined items from other materials and products. Any system replacing a physical quarantine should give equivalent security.

**3.15** Extra precautions should be taken in the processing and packaging of penicillins and other sensitizing products to ensure that there is no cross-contamination with other products. Air handling systems in areas where above products are handled should be completely separated from those systems in areas handling other drug products.

**3.16** Production areas should not be used as a general right of way for personnel or materials, or for storage(except of materials in process).

**3.17** Pipe work, light fittings, ventilation points and other services in manufacturing areas should be sighted to avoid creating uncleanable recesses. Services should preferably run outside the processing areas. They should be sealed into any walls and partitions through which they pass.

**3.18** Potable water in premises must be put under continuous positive pressure through a system free from defects. It has to conform with the approved standards of drinking water.

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

**3.20** Weighing of starting materials should be carried out in separate weighing areas designed for that use and with provisions for dust control.

**3.21 Environment**

Microbial and particulate quality is of importance in the manufacture of sterile and non-sterile products. It is necessary to monitor production areas regularly for absence of micro-organisms and for particulate levels to ensure that the environment is of satisfactory level for manufacture.

# 4. EQUIPMENT

**4.1 Principle**

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

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

**4.3** Equipment should be kept or stored in a clean condition and be checked for cleanliness prior to each use.

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

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

**4.6** Equipment used for weighing, measuring, testing and re-cording should be subject to regular recorded checks for accuracy and working order, according to written planned maintenance schedule. Periodic comprehensive checks can use-fully be supplemented by frequent simple checks on zero reading and accuracy.

**4.7** Control laboratory equipment and instruments should be suitable to the testing procedure undertaken.

**4.8** Fixed pipework (and valves) should be clearly labeled to indicate the contents, and where applicable the direction of flow.

**4.9** All service piping and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adapters for dangerous gases and liquids.

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

**4.11 Automatic and Electronic Equipment**

Automatic and Electronic Equipment should not be put in use except after standardization and confirmation of its performance. There should be fixed program to assure the validity and calibration with the establishment of a record program.

# 5. MATERIALS

## 5.1 Principle

The manufacturing of finished products involves the use of materials such as active, inactive raw materials and packaging materials. Consequently, special precautions must be taken in handling, testing and storing.

## 5.2 Starting materials

**5.2.1** All incoming materials must be kept quarantined immediately after receipt until they have been released by Quality Control during which time they should be stored under appropriate conditions.

**5.2.2** The purchase of starting materials is an important issue that concerns staff (from production and Quality Control) who have sound knowledge of suppliers.

**5.2.3** The starting materials should be purchased from suppliers and preferably directly from manufacturers. Established specifications, handling of material and packaging requirements as well as complaint and rejection policy must be verified prior to commitment with the suppliers.

**5.2.4** Each delivery should be visually checked upon receipt for integrity of containers and corresponding material label.

**5.2.5** Each delivery batch of material should be assigned a reference number that will identify it throughout storage, during dispensing and processing. This number should clearly appear on the label. This will ease tracing of details on this delivery and the analytical records.

**5.2.6** Different batches delivered for any one material must be given different reference numbers and must be regarded separately in relation to sampling, testing and releasing. Each delivery must be sampled according to written procedures.

**5.2.7** Appropriate measures should be taken to assure that all containers of a delivery contain the correct material. Sampling and identity testing of the material in each container can provide the necessary assurance. However, lesser sampling can be done when the supplier's range of materials is limited, or to depend on the reliability of the supplier and past experience or when the manufacturer's own process or quality control testing will reveal the wrong material.

**5.2.8** Status label should be issued by quality control personnel only. Status label should be changed in accordance with actual status of material.

**5.2.9** The label must carry the name of starting material designated in the specification. Any unauthorized abbreviations or other names must not be used.

**5.2.10** Starting materials in stores should be inspected at intervals by resampling at the retest date given in the starting material specifications.

**5.2.11** Only starting material that have been released by Quality Control can be used by production, such release should be by written instructions.

**5.2.12** Dispensing of starting material should be done by authorized personnel in accordance with written procedures to ensure that the correct materials are accurately weighed using clean, properly labeled containers. The reference number must be documented for each material upon dispensing.

**5.2.13** Proper measures must be taken to avoid cross contamination during dispensing.

**5.2.14** Materials dispensed for a production batch must be kept together and labeled accordingly.

## 5.3 Packaging materials:

**5.3.1** Packaging materials, primary and printed, should be dealt with as for starting materials in terms of:

**I-** Complying with written specifications.
**ii-** Each delivery must be given reference number.
**iii-** Holding in quarantine, sampling, testing and releasing by Quality Control.

**5.3.2** Packaging materials should be stored in closed containers in such a way as to prevent mix-ups.

**5.3.3** Any canceled packaging material must be disposed of promptly.

## 5.4 Intermediate and bulk products:

**5.4.1** Intermediate and bulk products should be properly labeled and stored under appropriate conditions.

**5.4.2** The purchase of intermediate and bulk products must be treated as for starting materials.

## 5.5 Finished products:

**5.5.1** Finished products must be held under quarantine prior to release by quality control.

**5.5.2** The testing and necessary control of finished products together with its batch records must be evaluated prior to releasing as described in section (14) under Quality Control.

## 5.6 Rejected and recovered materials:

**5.6.1** Rejected materials and products must be identified and stored under a quarantine system designated to prevent their use in manufacturing.

**5.6.2** Rejected materials should either be returned to the suppliers or destroyed. The action must be approved by authorized personnel.

**5.6.3** Reprocessing of products must be done only in exceptional cases and only permitted if the final quality is not affected. Written defined procedures must be established and approved by Quality Control and records of reprocessing must be kept.

**5.6.4** Reprocessed batch must be given a new batch number.

**5.6.5** The incorporation of recovery material conforming to specifications to a new batch is only permitted at a predetermined stage, carried out in accordance with written procedures and must be authorized beforehand.

**5.6.6** Quality Control must verify by additional testing if necessary a new reprocessed batch or the addition of recovery material to a batch.

## 5.7 Recalled products:

**5.7.1** Product recalled from the market must be stored separately and securely. (see section 13)

## 5.8 Returned products:

**5.8.1** Products returned from the market must be destroyed unless examination, testing and critical assessment by Quality Control prove the drug product meets appropriate standards of safety, identity, strength, quality and purity.

**5.8.2** A returned drug product can be reprocessed provided the subsequent drug product meets the appropriate specifications.

**5.8.3** Records of returned drug product must be maintained clearly showing product dosage form, batch number, reason for return, quantity returned, date returned and the final action taken.

## 5.9 Reference standards:

**5.9.1** Reference standards are the official reference standards and must be stored in secure area. Reference standards from producers must be tested, released, and kept in a secure area.

**5.9.2** Working standards can also be established as in-house reference standards. The latter are based on official reference standards when possible.

**5.9.3** In-house working standards should be stored separate from general laboratory reagents and must be rechecked at regular intervals.

## 5.10 Reserve samples:

**5.10.1** Reserve samples (of the necessary quantity) from each starting material delivery and finished product must be kept to perform all tests required.

**5.10.2** Reserve sample that represents each batch manufactured must be retained for one year after the expiration date.

**5.11 Waste materials:**

**5.11.1** Waste material which are toxic and flammable must be stored in separate storage area awaiting disposal.

**5.11.2** Waste materials must be disposed of safely and should not be allowed to accumulate.

**5.12 Miscellaneous:**

**5.12.1** All insecticides, fumigating agents and sanitizing materials should be used in such a way as to avoid contamination in production areas and stores.

* **Reagents and Culture Media:**

Reagents and Culture Media must be prepared according to written standard operating procedures. They must be properly labeled to indicate concentration, standardization factor, shelf life and storage conditions..

***Gases:**

Gases which come into contact with the pharmaceutical products must be considered as materials.

- Each cylinder must be tested for identification and correct color code.

-Correct storage conditions and frequent checking of pressure gauges must be maintained.

***Hazardous Material:**

there must be documented procedures for handling, sampling and Disposal of hazardous materials.

-Hazardous materials should be stored in well-ventilated areas and the environment must be properly monitored.

-People who come into contact with these materials must be properly trained and monitored and must wear protective clothing.

***Material storage:**

Material storage must be according to a documented list specifying the storage conditions and sampling / dispensing precautions. ( see section 16 )

# 6. VALIDATION

## 6.1 Concept and objective :-

Validated manufacturing process is one which has been proved to do what it purports or is represented to do . The proof of validation is obtained through the collection and evaluation of data , preferably, beginning from the process development phase and continuing through into the production phase. Basis of process validation includes :-

a. Calibration, verification and maintenance of equipment .
b. Qualification and / or validation of both process and equipment .
c. Challenge. Audit, monitor, or sample the recognized critical or key steps in the process .
d. Requalification or revalidation .

## 6.2 Process validation :-

*Assessments of the need for validation should be undertaken either by a team set up to monitor validation activities or by the person or organizational unit responsible for quality control. In any event, the person responsible for quality control should be represented in the decision making processed involved in validation .

*The validation protocol should be prepared by the technical personnel responsible for carrying out the validation exercise. It should state the way in which the process is to be operated, identify the controls to be exerted, specify the variables to be monitored , state the samples to be taken for subsequent testing, specify the product performance characteristics / attributes to be monitored along with acceptable limits and refer to the test methods to be used .

## 6.3 Prospective validation :-

Prospective validation is establishing documented evidence that a system does what is purports to do based on a preplanned protocol .

Prospective validation makes validation an integral part of a carefully planned, logical product / process developmental program .

There are four key elements that from the basis of a prospective process validation program .

1- Definition of the desirable attributes of the drug product or components thereof as well as those characteristics that are not desired .
2- Establishment of limitations or constraints for these attributes .
3- Determination of the controls or testing parameters that will be measured or tested .

4- Initiation of studies to establish control or boundary limits for those key attributes that influence the product process, quality and performance .

## 6.4 Certification :-

* Validation reports should give a comprehensive explanation of the work carried out and should include the clause for the process variables measured together with any in-process control results obtained . They should also incorporate results obtained on examination of the product for compliance with its specification - and performance standards. Where raw data are not included , reference should be made t the sources used and where they can be found .

* Any work done in addition to that specified in the protocol or any deviation from the protocol should be formally noted along with a justification .

* The review of results may either be carried out by the team appointed for the purpose or by the technical personnel responsible for the validation data must be carried out in conjunction with the person responsible for quality control . On completion of the review and completion of any corrective actions / repeated work, the result of the validation exercise must be formally recorded as being either accepted or rejected .

* The team carrying out the review should also make written recommendations on the extent of monitoring and in-process controls necessary for routine production. These should include details of the methods, limits and frequencies and of the actions to be taken when limits are exceeded. consideration should be given at this stage to the need for any alterations to the finished product or raw materials specifications .

* Setting of criteria for revalidation, maintenance and calibration should be the final step in the validation process where the reviewing team should specify the interval or conditions that will necessitate re-validation. This should also include recommendations for maintenance and calibration to be carried out on the process plant and related utilities .

## 6.5 Revalidation :-

* Whenever there is a change in a validated process or in any of the main factors affecting product quality consideration should be given as the whether revalidation is necessary. This should happen through a formal system and the necessary revalidation work should be organized, carried out and reported in the same way as initial validation.

* Certain processes may require a level of routine monitoring which may equate to revalidation . In this case the same protocol can be used on each occasion that the process is checked. An example of this would be the routine monitoring of aseptic process by stimulated processing and filling trials .

## 6.6 Retrospective validation :

* Retrospective process validation involves the use of historical data to provide the necessary documentary evidence that a process does what it purports to do . The sequence of events in the validation system may differ but will still involve the preparation and review of a protocol , the reporting of results abstracted from accumulated data , the review of the report and conclusions and recommendations .

*The sources of information for this activity will include batch records and process control charts along with analytical and storage stability results .

## 6.7 Product Release-Additional Requirement for Validation batches :-

*There should be a system which ensures that products made by new or altered processes are not released for sale until quality control procedures are complete and the results of successful validation reported . In practice this may be incorporated in the formal batch release procedure particularly where periodic revalidation or monitoring is necessary .

*Regulatory requirements must be taken into account when assessing the acceptability of batches made for the purpose of process validation .

# 7. SANITATION AND HYGIENE

## 7.1 Principle

A high level of hygiene should be reached and maintained in the manufacturing areas to keep products safe and prevent them from any possible contamination. Sanitation and hygiene covers personnel, premises, equipment, product material and containers, products for cleaning and disinfecting and anything that could become a source of contamination.

## 7.2 Personnel hygiene:

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

**7.2.2** Every person entering the manufacturing areas should wear protective garments appropriate to the operation to be carried out (head gear, beard covers, overall with minimum number of pockets, or suitably designed, gloves, shoe covers, masks and safety goggles).

**7.2.3** Operators in sterile areas must change prior to leaving the area, and this may be desirable for some other areas especially to minimize potential cross contamination.

**7.2.4** In aseptic areas, personnel should wear sterilized single or two piece suits, gathered at the wrists and ankles and with high necks. Head gear must totally enclose hair of head and footwear should totally enclose the feet, and trousers bottom should be tucked inside the footwear.

**7.2.5** The clothing and its quality should be appropriate for the process and the working area and worn in such a way as top protect the product from contamination. Garments should regularly be changed, not worn outside the factory premises.

**7.2.6** Direct contact should be avoided between the operator's hands and starting materials, intermediate and bulk products.

**7.2.7** Hand washing and hygiene drying facilities should be conveniently available.

**7.2.8** Wrist watches and jewelry other than a simple wedding ring should not be worn. Cosmetics which can shed particles should not be used.

**7.2.9** Changing and washing should follow a clearly displayed written procedures.

**7.2.10** Laundry must be available for washing garments used for sterile and other special products.

**7.2.11** Eating, drinking, chewing or smoking, storage of foods, drinks, smoking materials, and plants in the production and storage area should be prohibited.

**7.2.12** Personnel working in sterile area should be provided with clean sterilized protective garments at each work session, or at least once a day if monitoring results justify this. Gloves, should be regularly disinfected during operations. Masks and gloves should be changed at least every working session. The use of disposable clothing may be necessary in certain circumstances.

**7.2.13** Visitors or untrained personnel should, preferably, not to 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 and they should be closely supervised.

### 7.3 Medical check and personnel health requirements

**7.3.1** Pre-employment examination must be done and annual medical reexamination is sometimes required.

**7.3.2** Those who feel fit for work but show symptoms of common cold or other non-disabling illness, should be allowed to work at tasks in which they cannot contaminate products.

**7.3.3** An employer has a responsibility to protect the employee from unacceptable exposure to the materials being handled, especially which have physiological properties.

**7.3.4** Any person shown at any time (either by medical examination or by supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug products containers, closures or in-process materials.

**7.3.5** Staff must report on health condition to supervisory personnel.

### 7.4 Cleanliness and hygiene:

**7.4.1** Clean, aseptic and other related processing areas should be cleaned frequently and thoroughly in accordance with a written program approved by Quality Control Department. Where disinfectants are used, different types should be employed in rotation to discourage the development of resistant strains of microorganisms.

**7.4.2** Disinfectants and detergents used should be monitored for microbial contamination. Dilutions should be kept in previously cleaned containers and should not be stored unless sterilized.

**7.4.3** Areas should be frequently monitored microbiologicaly by means of 'settle' plates, surface sampling or any other suitable mean. Appropriate action must be taken as soon as results deviate significantly from those usually found in the area concerned. Fumigation may be useful for reducing microbiological contamination in inaccessible places.

**7.4.4** Cleaning program and cleaning procedures (rooms, equipment, facilities,...) should be achieved and recorded.

**7.4.5** Dry sweeping is forbidden (could be vacuum cleaning, wet cleaning) and any method should be identified and specified.

**7.4.6** Separate mops should be used according to processing stage or as necessary.

**7.4.7** All cleaning materials, equipment, utensils used must be cleaned and stored in suitable condition.

**7.4.8** Areas should be kept free from insects and rodents. Insect killers can be used for this purpose.

## 7.5 Premises

**7.5.1** Layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and any adverse effect on the quality of product.

**7.5.2** Premises should be cleaned and where applicable disinfected.

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

**7.5.4** Premises should be situated in an environment which presents minimum risk of contamination of materials or products.

**7.5.5** Sterile medicinal products should be prepared in specially designed and constructed manufacturing department which is separated from other manufacturing areas. Different operations such as component preparation, filling and sterilization are effectively segregated from one another.

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

**7.5.7** Waste materials should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings, and disposed off at regular and frequent intervals. Special care is necessary over the disposal of waste containing dangerous or highly toxic waste.

**7.5.8** Changing rooms should be designed as air locks and used to provide separation of the different stages of changing and to minimize microbial and particulate contamination of protective clothing.

**7.5.9** Hand washing facilities should be provided only in the changing rooms.

**7.5.10** Sinks and drains should be avoided whenever possible and should be excluded from areas where aseptic operations are performed. Where installed, they should be designed, located and maintained so as to minimize the risk of microbial contamination. They should be fitted with effective, easily clean-able traps and with air breaks to prevent back flow. Any floor channel should be open, shallow and easily cleanable and be connected to drains outside the area in a manner which prevents ingress of microbial contamination.

## 7.6 Equipment

**7.6.1** Manufacturing equipment should be designed so that they can be easily and thoroughly cleaned. They should be cleaned according to detailed written procedures, stored in clean and dry conditions.

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

**7.6.3** All equipment must be inspected for cleanliness immediately before any operation.

**7.6.4** When used for different formulations, the equipment must be thoroughly cleaned at the end of processing each drug product.

**7.6.5** Distilled or deionized water and other water pipes should be sanitized according to suitable written procedures.

**7.6.6** Cleaning and sanitation procedures must be properly documented and validated as necessary.

**7.6.7** Where dedusting procedures are utilized, they should involve vacuum.

**7.6.8** Damp equipment should not be left for any significant length of time before use. It may need to be dried or rinsed prior to use.

## 8. DOCUMENTATION

### 8.1 Principle

Documentation is an essential part of the quality assurance system. Its purposes are to define the system of manufacture and control, to ensure that personnel concerned in all activities of drug manufacture are fully informed, instructed and follow the relevant procedures and that authorized persons are fully informed of the complete history of each batch of the product and to provide an audit trail that will permit investigation of any suspected defective product.

### 8.2 General

**8.2.1** Documents should be designed, prepared and distributed with care for easy, proper and effective use.

**8.2.2** Documents should be approved, signed and dated by the appropriate authorized persons. A list of authorized initials and signatures should exist and kept updated.

**8.2.3** Documents should contain all necessary, but no superfluous data. They should be reviewed, updated or amended as necessary and approved by the appropriate authorized persons.

**8.2.4** Where a document has been revised and authorized, a copy should be retained for reference. Systems should prevent inadvertent use of superseded documents.

**8.2.5** Documents should have unambiguous content; title, nature and purpose should be clearly stated.

**8.2.6** Documents bearing instructions should be written in the imperative, as numbered steps. They should be clear, precise, unambiguous and written in a language that the user can easily understand.

**8.2.7** Documents should be readily available to all concerned and for authorized inspection during the retention period at the establishment where the activities described in such records occurred.

**8.2.8** Documents which require the entry of data (records) should provide sufficient space for the entry. Entries should be clear, legible and indelible.

**8.2.9** Any alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

**8.2.10** Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable.

## 8.3 Documents required

### 8.3.1 Specifications and testing procedures:

**General**

- There should be appropriately authorized and dated specifications, including tests on identity, content, purity and quality for starting and packaging materials and finished products; where appropriate, they should be available for intermediate or bulk products.

- Each specification and testing procedure should be drafted by the appropriate organizational unit and reviewed and approved by the Quality Control Unit.

- Each specification should be periodically reviewed to comply with new editions of official compendia or other well established specifications.

#### 8.3.1.1 Specifications and testing procedures for starting material:

8.3.1.2 Each specification should be dated and include:

**a)** A designated name and an internal reference code unique to the material.
**b)** A reference to pharmacopoeial monograph, where applicable.
**c)** A reference to any alternative proprietary designation of the material.
**d)** A description of the physical form of the material.
**e)** Tests and acceptance limits for qualitative and quantitative requirements with details of or reference to the test methods to be used.
**f)** Safety precautions.
**g)** Storage requirements.
**h)** Frequency of retesting the stored material, if required.
**i)** Specific tests necessary for reassessment of an expired material if an extension of expiration date is possible.
**j)** The suppliers and the original producer of the materials or a reference for, if any.
**k)** Sampling procedure or instruction of a reference to procedures.

#### 8.3.1.2 Specifications and testing procedures of packaging material:

Each specifications should be dated and include:

**a)** A designated name and an internal reference code unique to the packaging material.
**b)** A description of the type of packaging material, thickness, dimensions, colors, strength and printed text, as applicable.
**c)** Technical drawings, where applicable.
**d)** Tests, examinations and acceptance limits for determining compliance with the specifications.
**f)** Safety precautions, if applicable.
**f)** Storage requirements, if applicable.
**g)** Frequency of reexamination or reinspection of the stored packaging material, if required.
**h)** The supplier of the packaging material or a reference for, if any.

**i)** A specimen of printed material.
**j)** Sampling procedures or instructions of a reference to procedures.

#### 8.3.1.3 Specifications for intermediate and bulk product:

Specifications for intermediate and bulk product should be available if these are purchased or dispatched, or if data obtained from intermediate products are used in the evaluation of the finished product. The specifications should be similar to those for starting materials or for finished products, as appropriate.

#### 8.3.1.4 Specifications for finished products:

Each specification should be dated and include:
**a)** The designated name of the finished product and the code reference, if applicable.
**b)** The designated name of the active material and dosage form and strength of the product.
**c)** A reference to pharmacopoeial monograph when applicable.
**d)** Finished product physical description and a reference to container and package details.
**e)** Tests and acceptance limits for qualitative and quantitative requirements with details of, or reference, to the test method to be used.
**f)** Safety precautions.
**g)** Storage requirements.
**h)** Frequency of reexamination or retesting of the stored finished products.
**i)** The shelf life of the product.
**j)** Sampling procedure or instructions or a reference to procedure.

### 8.3.2 Master formula and processing procedure (or method):

A master formula should exist for each product and batch size to be manufactured.
The master formula and processing procedure, including any changes, should be drafted, reviewed and approved by the appropriate organizational units and reviewed and approved by the quality control unit.
The master formula and processing procedure should be dated and include:
**a)** The product name, with a reference code relating to its specifications.
**b)** A description of the pharmaceutical dosage form, strength and batch size.
**c)** The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product, and a statement of the total weight or measure of any dosage unit.
**d)** A complete list of starting materials, designating the names, their unique reference codes, and amounts of each, whether or not they appear in the finished product, using the same weight system of each starting material.
**e)** A statement concerning any calculated excess of starting material used in the process.
**f)** A statement of theoretical weight or measure at appropriate phases (stages) of processing.

**g)** A statement of theoretical field, including the maximum and minimum percentages of theoretical yield (depends on definitions).
**h)** A statement of the processing location and the principal or major equipment to be used.
**i)** The methods, or reference to the methods, to be used for preparing the critical (major) equipment, e.g. cleaning assembling, calibrating, sterilizing.

**j)** The details of any in-process controls with their limits and sampling instructions.
**k)** Detailed stepwise processing instructions (e.g. checks on materials, pretreatment, sequence for adding materials, mixing times, temperatures).
**l)** Requirements for bulk storage of the product, including containers, labels and any special storage conditions.

### 8.3.3 Master packaging procedures:

A master packaging procedure should exist for each product, pack size and type. The master packaging procedure including any changes, should be drafted, reviewed and approved by the appropriate organizational units and reviewed and approved by the quality unit. The master packaging procedure should be dated and include or have reference to:

**a)** The product name.
**b)** A description of its pharmaceutical form, strength and method of application where applicable.
**c)** The pack size expressed in terms of the number, weight, or volume of the product in the final container.
**d)** A complete list of all the packaging materials designating the names, their unique reference wide, quantities, sizes, and types.
**e)** Where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number, manufacturing and expiry dates of the product have been marked.
**f)** Special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before operations begin.
**g)** A description of the packaging operation, including any significant subsidiary operations, and equipment to be used.
**h)** Details of in-process control with instructions for sampling and acceptance limits.
**i)** Procedure for reconciliation of the issued quantities of bulk product and packaging material with the number of unit packs produced.
**j)** Statement of the theoretical yield and percentage of the actual yield.
**k)** A description of containers, closures and other packaging material including a specimen of the product label and other labeling material signed and dated by the authorized person(s) responsible for approval of such labeling.

### 8.3.4 Batch processing records:

Batch processing records should be prepared and kept for each batch of drug product produced and should include complete information relating to the production and control of the batch.

The batch processing record is reproduced from its currently approved master processing procedure and should be checked for accuracy, dated and signed. The method used for reproduction should avoid transcription errors.

The batch processing record should show that each stage has been accomplished and entered at the time of performance (sign). Any deviation from the written procedure should be recorded and justified.

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

The batch processing record shall be dated and includes or documents:

**a)** Product name, batch number, unique reference code number and the specific identification number of each batch of starting material or in-process material used, including the batch number and amount of any recovered or reprocessed material added)

**b)** Weights and measures of the starting materials used in the course of processing.

**c)** Dates and times of commencement of significant intermediate stages and of completion of production.

**d)** Identification of the person(s) performing and directly supervising or checking each significant step in the operation.

**e)** The name and signature of the person responsible for each stage of production.

**f)** Any relevant processing operation or event and the major equipment used identified by a distinctive identification number or code. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.

**g)** The in-process and laboratory controls performed, the initials of the person(s) carrying them out, and the results obtained.

**h)** A statement of the actual yield and a statement of the percentage theoretical yield at appropriate phases of processing .

**i)** Any sampling performed during various steps of processing including the quantities taken.

**j)** Notes on special problems including details, with signed authorization for any deviation from master formula.

**k)** Results of investigation for non compliance of processing and control records with written approved procedures (specific process failure, yield discrepancies).

### 8.3.5 Batch packaging records:

Batch packaging records should be prepared and kept for each batch of drug product produced and should include information relating to the packaging and control of the batch.

The batch packaging record is reproduced from its currently approved master packaging procedure and should be checked for accuracy, dated and signed. The method used for reproduction should avoid transcription errors.

The batch packaging record should show that each step has been accomplished and entered at the time of performance, with date and signature of the responsible person.

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

The batch packaging record shall be dated and include or documents:

**a)** Product name, batch number, quantity of bulk product to be packed, unique reference code number and the specific identification number of each batch of packaging material.
**b)** The weights and measures of the packaging materials used in the course of packaging.
**c)** Dates and times of commencement and completion of significant packaging stages and of completion of packaging operation.
**d)** Identification of the persons performing and directly supervising or checking each significant step of the operation.
**e)** The name(s) and signature(s), of the person(s) responsible for each significant stage of packaging.
**f)** Details of any relevant packaging operation and the major packaging lines used, identified by a distinctive identification number or code. In cases where only one of a particular type of equipment may exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.
**G)** The in process and laboratory controls results and the checks made for identity and conformity with the packaging instructions.
**h)** Any sampling performed during and after packaging including the quantity taken.
**i)** Samples of the printed packaging materials used, including specimens with the batch number, manufacturing and expiring date and any additional overprinting.
**j)** Notes on special problems including details, with signed authorization for any deviation from the packaging.
**k)** The instruction for keeping the product unpacked or the record of returning the unpacked product to the storage area
**l)** The quantities of all packaging material and bulk product issued, used, destroyed, or returned to stock and the quantities of product obtained and the reconciliation.

### 8.3.6 Standard operating procedures and records

#### 8.3.6.1 Standard operating procedure for sampling

There should be standard operating procedure for sampling, specifying the person(s) or unit authorized to take samples.

The procedure should include the following.

**a)** Method of sampling, the sampling plan and standard used in the sampling plan.

**b)** Equipment and type of sample container(s) to be used.

**c)** Precautionary measures taken during sampling including use of special clothing by the person(s) taking the sample.

**d)** Location of sampling.

**e)** Quantity of sample(s) to be withdrawn.

**f)** Method of subdividing the sample taken, if required..

**8.3.6.2 Record of sampling**

A record of sampling should be prepared in accordance with the approved standard operating procedure for sampling.

**8.3.6.3 Test methods**

There should be written procedure for inspecting and testing of starting materials, intermediate, bulk and finished products, describing the method, reagents and equipment to be used.

**8.3.6.4 Record of analysis and test report**

**8.3.6.4.1** A record of analysis and test report should be prepared for each batch or lot of starting material, packaging material, contract manufacture material, intermediate, bulk and finished product following the approved test method.

**8.3.6.4.2** The record of analysis should contain at least the following data:

**a)** The name of the material or product and, where applicable, dosage form.

**b)** The batch number and, where appropriate, the manufacturer and/or supplier.

**c)** Reference to the relevant specifications and testing procedures.

**d)** test results, including observations and calculations, and reference to any specifications (limits).

**e)** Dates of testing .

**f)** The initials of the persons who performed the testing.

**g)** The initials of the persons who verified the testing and the calculations, where appropriate.

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

**i)** A cross reference to any relevant certificate of analysis.

**Note:** A sample of the starting material of final packaged product sufficient in size to permit analytical re-examination should be retained as part of the starting material record.

**8.3.6.5** There should be standard operating procedure and records for the receipt of each delivery of starting material and packaging material.

**8.3.6.5.1** The record of the receipt should include:

**a)** The name of the material on the delivery note and the container:

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

**8.3.6.6** There should be standard operating procedure and records for the inventory of each product.

**8.3.6.6.1** The record should contain the following data:
**a)** Product name and batch number.
**b)** Date or receipt.
**c)** Quantity received.
**d)** Batch number.
**e)** storage conditions.

**8.3.6.7** Records should be maintained for the distribution of each batch of a product to facilitate the recall of batch, of necessary.

**8.3.6.7.1** The distribution record should contain the following data:
**a)** Name and address and number of receiver.
**b)** Delivery order date and number.
**c)** Name, dosage form and strength of the product.
**d)** Quantity delivered.
**e)** Product batch number.
**f)** Expiration date, where applicable.
**g)** Special storage requirements or precautionary measures to handle the product.

**8.3.6.8** There should be standard operating procedure for the handling of product complaints. Complaints record should include the definition of product complaints and adverse reactions, the type of complaint and report, method of handling and evaluation of the complaint and report.

**8.3.6.8.1** The record of product complaint, and adverse reactions report should contain the following data:
**a)** Product name and batch number.
**b)** Type of complaint or report.
**c)** Source of complaint or report.
**d)** Sample of complaint or reported product.
**e)** Summary of complaint or report.
**f)** Result of investigation.
**g)** Evaluation of complaint or report.
**h)** Response and follow up action to the complaint or report.

**8.3.6.9** There should be standard operating procedure for the handling of returned drug product. This procedure should include the guidelines for making decision either to salvage, reprocess, or destroy the returned drug product. The handling and disposition of returned drug product should be documented.

**8.3.6.10** There should be standard operating procedure for the finished product recall from market. The product recall should be documented.

**8.3.6.10.1** The product recall should contain the following data:

- **a)** Product name, batch number and batch size.
- **b)** Date of starting and completing the product recall
- **c)** Reason of recall.
- **d)** Warehouse stock and distributed stock of the product being recalled at the start of recall.
- **e)** Quantity of recall product returned from the market.
- **f)** Source of returns.
- **g)** Evaluation of product recall.
- **h)** Follow up action taken.
- **i)** Report on the handling of product recall to the management and to the government authority, if required.

**8.3.6.11** There should be standard operating procedure for the destruction of rejected material or product. The destruction should be recorded.

**8.3.6.11.1** The record should include the following data:

- **a)** Product name, batch number and quantity of rejects.
- **b)** Source of rejected material or product.
- **c)** Method of destruction.

**8.3.6.12** There should be standard operating procedure for the maintenance, cleaning and monitoring of manufacturing areas and equipment, for pest control and for monitoring airborne particles and/or violent microorganism in specific areas.

- **a)** A procedure for maintenance and cleaning of each piece of equipment should be available. This procedure should include the job description and maintenance schedule. The maintenance and cleaning of an equipment, including the repair job and replacement of equipment parts should be re-corded.
- **b)** A procedure for cleaning a production equipment should specify cleaning of the equipment prior to change of batch as well as change of product. The procedure should include the method of cleaning and the tools and cleaning materials to be used.

The cleaning operation should be documented and become part of the batch record.

**8.3.6.12.2** A procedure for cleaning of a manufacturing area should be available. This procedure should include the specific area to be cleaned, the tools and cleaning materials to be used and the time and schedule of cleaning. The cleaning operation should be documented.

**8.3.6.12.3** A procedure for pest control should be available. This procedure should include the scope and schedule of pest control, the method of control, the

tools and pesticide to be used, precautionary measures and the persons or units involved in the pest control. The pest control operation should be documented.

**8.3.6.12.4** A procedure for monitoring airborne particles and microorganisms in specific areas should be available. This procedure should include the method of monitoring, areas to be monitored, specifications including alert and action levels. The result of monitoring should be documented.

**8.3.6.13** There should be standard operating procedure for operating and calibrating specific equipment. A record should be maintained for the use and the calibration of such equipment.

**8.3.6.13.1** A procedure for operating a specific equipment is required to prevent mishandling of the equipment that may influence the quality of a product utilizing the equipment or cause damage to the equipment. The procedure is normally adopted from the equipment manual.

**8.3.6.13.2** A procedure for calibrating a specific equipment is required to ensure that the equipment always weighs or measures accurately. The procedure should include the calibration schedule, reference standard, reagents and tools to be used and the method of calibrating or the reference manual used for calibrating the equipment. The calibration performed and its result should be documented.

**8.3.6.14** There should be a standard operating procedure describing the details of the batch numbering system, with the objectives of ensuring that each batch of intermediates bulk, or finished product is identified with specific batch number.

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

**8.3.6.14.2** The standard operating procedure for batch numbering should assure that the same batch numbers will not be repeatedly used, this applies also to reprocessing.

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

# 9. Production

## 9.1 Principle

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

## 9.2 General

**9.2.1** Handling of materials and products, such as receipt and quarantine, sampling, storage, labeling, dispensing, processing, packaging and distribution should be done in accordance with written procedures.

**9.2.2** Any deviation from procedures should be avoided. If deviation occurs, it should be approved in writing by an authorized person(s).

**9.2.3** The final yield, and any significant intermediate yield, of each production batch should be recorded and checked against the theoretical yield. In the event of significant variation, steps should be taken to prevent release or further processing of the batch (and of any other associated batches or products processed concurrently and with which it may have become admixed), until an adequate explanation which does not prevent release or further processing is given.

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

**9.2.5** At all times during processing, all materials, bulk containers, major equipment, and where appropriate the rooms used should be labeled. Where applicable, the label indicated should also mention the stage of production.

**9.2.6** Access to production premises should be restricted to authorized personnel.

**9.2.7** When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust.

**9.2.8** Contamination of a starting material or of a product by another material or product has to be avoided.

**9.2.9** Production areas where products susceptible to micro organism growth are processed, should undergo periodic microbiological monitoring.

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

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

**a)** Production in segregated areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations and certain other biologicals), or by campaign (separation in time) followed by appropriate cleaning.

**b)** Providing appropriate airlocks, pressure differentials, and air extraction.

**c)** Minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air.

**d)** Wearing protective clothing in areas where products with special risk of cross-contamination are processed.

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

**f)** Using a "closed system" of production.

**g)** Testing for residues.

**h)** Using cleanliness status labels on equipment.

## 9.3 Processing

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

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

**9.3.3** Provisions should be implemented to indicate failures of an equipment or service to an equipment. Defective equipment should be withdrawn from use until the defect has been rectified.

**9.3.4** Production equipment should be cleaned according to detailed and written procedure and stored only under clean and dry conditions.

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

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

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

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

**9.3.9** Measuring weighing, recording, and control equipment and instruments should be serviced and calibrated at pre-specified intervals and records maintained. Pre-check of the instrument to ensure its satisfactory functioning should be conducted daily or prior to using the instrument or whenever necessary.

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

## 9.4 Packaging

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

**9.4.2** Before packaging operations are started, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents previously used, if these are not required for the current operation.

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

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

**9.4.5** The correct performance of any printing operation done separately or in the course of the packaging process must be checked and recorded. Attention should be paid to printing by hand, which should be rechecked at regular intervals.

**9.4.6** Special care should be taken when using cut-labels and when over printing is carried out off-line and in hand-packaging operations. Roll-feed labels are normally preferable to cut-labels, in helping avoid mix-up. One hundred percent on-line verification by automated electronic means can be helpful towards preventing mix-up. However, checks should be made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

**9.4.7** On line control of the product during packaging should include at least checking the following:

**a)** General appearance of the packages.
**b)** Whether the packages are complete.
**c)** Whether the correct products and packaging materials are used.
**d)** Whether any over printing is correct.
**e)** Correct incoming of line monitors.

**9.4.8** Prior to packaging and labeling of a given batch of a drug, the batch processing records should show that the batch has been duly tested and approved for packaging by the quality control unit.

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

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

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

## 9.5 Recovered materials

Materials may be reworked, recovered or salvaged by an appropriate and authorized method, provided that the material is suitable for such reprocessing, that the resultant product meets required specifications and that there is no significant changes in product quality; stability tests should be conducted as necessary and documentation should accurately record that reworking process was carried out.

# 10. QUALITY CONTROL

## 10.1 Principle

Quality control is concerned with sampling, specifications, and testing and with the organization, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

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

**10.3** The responsibilities and procedures applicable to the quality control department should be in writing and such written procedures should be followed. This section should be considered closely with section 1.4

## 10.4 Sampling

**10.4.1** Samples should be representative of the batch of material from which they are taken in accordance with the approved written procedures.

**10.4.2** Sampling should be carried out so as to avoid contamination or other adverse effects to the quality. Some particularly hazardous or potent materials may require special -care.

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

**10.4.4** Each sample container should bear a label indicating the name of the starting material, batch or lot number, reference number, the number of container from which the sample has been taken, date of sampling and the signature of the person who takes the sample. It should be possible to identify the bulk containers from which the samples have been drawn.

## 10.5 Specifications

**10.5.1** Specifications approved by quality control should be established for all starting materials, packaging materials and bulk, intermediate and finished products.

## 10.6 Testing

**10.6.1** Testing methods should be validated. Complete re-cords for established methods and their modifications employed in testing, standardization of laboratory reference standards, solutions, periodic calibration for laboratory instruments, gauges and recording devices.

**10.6.2** Upon receipt and before acceptance, each container or grouping of containers or components, drug product containers and closures, should be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination. They should be stored under quarantine status until they have been tested or examined as appropriate.

**10.6.3** An identity test should be conducted on a sample from each container of starting material.

**10.6.4** With respect to printed packaging materials, each batch (lot) must be examined following receipt.

## 10.7 Releasing Starting and Packaging Materials

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

**10.7.2** In lieu of testing by the manufacturer, a certificate of analysis may be accepted from the supplier , provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results and through on site audits of the supplier's capabilities. However, identity test should be performed.

## 10.8 In-process control:

**10.8.1** To assure batch uniformity and integrity of the drug products, written procedures should be established describing the in-process controls and tests or examinations to be con-ducted on appropriate samples of in-process material of each batch. In-process control records should be maintained and form a part of the batch records.

## 10.9 Finished products

**10.9.1** For each batch of drug product, there should be appropriate laboratory determination of satisfactory conformance to its finished product specifications prior to release.

**10.9.2** Products failing to meet the established specifications or any relevant quality criteria should be rejected. Reprocessing may be performed if feasible after the review and approval of the quality control . Reprocessed product should meet all specifications and other quality criteria prior to its acceptance and release.

## 10.10 Production record review

**10.10.1** Production and control records should be reviewed and any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or

discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

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

## 10.11 Stability Studies

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

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

**10.11.3** A written program for on going stability determination should be developed and implemented to include elements such as:

**a)** Complete description of the drug involved in the study.
**b)** Complete testing parameters and methods describing all tests for potency, purity and physical characteristics and documented evidence that these tests are stability indicating.
**c)** Provision for the inclusion of a sufficient number of batches.
**d)** Testing schedule for each drug.
**e)** Provision for special storage conditions.
**f)** Provision for adequate sample retention.
**g)** A summary of all the data generated, including the evaluation and the conclusions of the study.

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

# 11. PRODUCTION OF STERILE PRODUCTS

## 11 Principles

Sterile products should be manufactured in separate areas with special care and attention, with the object of preventing and/or eliminating microbial and particulate contamination. Much of the work depends on the skill, training and attitude of the persons involved. The sterile finished products have to pass carefully the specified tests. Similarly in-process quality assurance assumes the same great importance.

## 11.1 General Consideration

**11.1.1** Sterile products may be classified broadly into two categories according to their way of production:-

- those which must be processed by aseptic means during all stages of processing; and
- those which are sterilized after being sealed in their final container (or terminally sterilized); wherever possible, sterile products should be terminally sterilized.

**11.1.2** All sterile products should be manufactured under carefully controlled and monitored conditions. Reliance should not be placed only on any terminal process or test for assurance of the microbial and particulate quality of the finished product.

**11.1.3** To assure sterilization process, special precautions should be taken to minimize the bioburden in the area and the product. The separate and closed area should be entered through an air-lock. The air supplying those areas should be filtered through microbial filters.

The areas where terminally sterilized products are manufactured should be designed so as to prevent possible mixing between sterilized products and those waiting for sterilization.

To assure sterility of products produced under aseptic conditions an extra precautions should be taken.

Specially designed and constructed sterile suite should be continuously supplied with air that is filtered through microbial filters of high efficiency creating differential pressure between different rooms so that the most critical room will be of the highest positive pressure. such filters have to be checked on installation and periodically thereafter.

All surfaces in manufacturing areas should be designed to facilitate cleaning and disinfection. Routine microbial counts of the air in the areas described above should be carried out before and during manufacturing operations. The results of

such counts should be checked against established standards and adequate records of the counts should be maintained.

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

**TABLE 1**

**AIR CLASSIFICATION SYSTEM FOR MANUFACTURE OF STERILE PRODUCTS**

| | **MAXIMUM NUMBER OF PARTICLES PERMITTED PER $M^3$** | | **MAXIMUM NUMBER OF VIABLE MICROORGANISM PERMITTED PER $M^3$** |
|---|---|---|---|
| **GRADE** | **0.5 - 5 μm** | **> 5 μm** | |
| **A (laminar air flow workstation)** | 3500 | NONE | LESS THAN 1 |
| **B** | 3500 | NONE | 5 |
| **C** | 350 000 | 2 000 | 100 |
| **D** | 3 500 000 | 20 000 | 500 |

## 11.2 Definitions

The following definitions , some of which are additional to those given in the glossary, are specially significant in the context of sterile production.

**11.2.1** **Air lock:** As defined in glossary.

**11.2.2** **Aseptic Area:** A room, suite of rooms or special area within a Clean Area (see below) designed, constructed, serviced and used with the intention of preventing microbial contamination of the product.

**11.2.3** **Batch:** As defined in glossary, with the further proviso that for the purpose of a sterility test, a batch is a collection of sealed containers prepared in such a manner that the risk of microbial contamination may be considered the same for each of the units in it, it is usually:

**a)** One sterilizer load, or

**b)** The quantity of containers filled aseptically in one working session at one work station.

(In the case of aseptically filled products which are subsequently freeze-dried should be one freeze drier load if this is less than in (b) above): A working session should be deemed to terminate whenever there is significant change in circumstances which could affect the risk of product contamination (for example, a change of filling equipment, a change in the team of operators or a machine break-down). What in fact constitutes a significant change should be documented and agreed in advance by the persons responsible for production and quality control.

**11.2.4** **Changing room**: A room or suite of rooms designed for the changing of clothes and from which a clean or aseptic area is entered.

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

**11.2.6** **Contained work station**: A small working area or enclosure with its own, usually unidirectional, filtered air supply.

## 11.3 Personnel (refer to section 2)

**11.3.1** Personnel working in clean and aseptic areas should be selected with special care to ensure that they are relied upon to observe the appropriate discipline and they are not subject to any disease or condition that would present any microbiological hazard to the drug product.

**11.3.2** Any person exhibiting bad hygienic habits should not work in those areas.

**11.3.3** High standard of personal hygiene and cleanliness is essential. Staff should be instructed to report any condition (e.g. diarrhea, cough, infected skin or hair, wounds, etc..) which may cause the shedding of abnormal numbers or type of organisms. Periodic health checks for such conditions should be performed.

**11.3.4** Only the minimum required number of personnel should be present in clean or sterile areas when work is in progress. Inspection and control procedures should be conducted from outside the area, as far as possible.

**11.3.5** Those who are employed in such areas, including those concerned with maintenance, should receive training in the discipline relevant to the successful manufacture of sterile drug products, including reference to hygiene and- at least- the basic elements of microbiology. They should be appropriately gowned.

## 11.4 Clothing

**11.4.1** Personnel entering clean or aseptic areas should change into special garments which include head and foot wear. These garments should shed no fibers or particulate matter and retain particles shed by the body. They should be comfortable to wear, and loose in order to reduce friction.
The garments should be restricted only for use in the relevant clean or aseptic areas.

**11.4.2** In aseptic areas, the personnel should wear sterilized single or two-piece trouser-suits, gathered at the wrists and ankles and with high necks. Head cover must totally enclose hair and beard, tucked into the neck of the suit. Footwear should totally enclose the feet, and trouser bottoms should be tucked inside the foot-wear.

**11.4.3** Wristwatches and jewelry should not be worn. Cosmetics should not be used.

**11.4.4** Clean and aseptic area clothing should be laundered, sterilized and thereafter handled in such a way that it does not gather contaminants which can later shed. Separate laundry facilities for these clothes is preferred.

## 11.5 Premises

**11.5.1** Sterile products should be prepared in specially designed and constructed manufacturing areas in which different types of operations - such as component preparation, solution preparation, filling and sterilization - are effectively separated from one another.

**11.5.2** The various processing rooms should be supplied and effectively flushed with air under positive pressure, which has passed through filters of appropriate designated efficiency and which will maintain positive pressure differential relative to surrounding areas.

**11.5.3** Non-sterile products should not be processed in the same area, and at the same time, as sterile products.

**11.5.4** Room temperature and humidity should be maintained at a level which will not cause excessive sweating of operators wearing protective garments.

**11.5.5** Access to the clean and aseptic areas should be restricted to authorized persons, who would enter only through gowning rooms where normal factory clothes are exchanged for special garment.

## 11.6 Cleanliness and hygiene

The clean and aseptic places, in addition to other related areas, should be cleaned frequently and thoroughly in accordance with a written program. Where disinfectants are used, different types should be employed in rotation to avoid development of resistant strains of micro-organisms.

## 11.7 Processing

**11.7.1** The starting materials should not contain significant levels of micro-organisms or pyrogenic material.

**11.7.2** Activities in the clean and aseptic areas should be kept to the minimum, movement of personnel should be con-trolled and methodical, to avoid excessive shedding of particles and organisms.

**11.7.3** The interval between the sterilization of equipment, containers and component and their use in an aseptic process, should be kept to the minimum.

**11.7.4** When a new aseptic process is introduced, when any significant change is made in such a processor in the equipment, when staff are being trained and at regular intervals thereafter, the efficacy of aseptic procedures should be validated, e.g. by filling a sterile liquid nutrient medium or powder and testing for the incidence of contamination. Such fillings should be carried out under normal operating conditions.

## 11.8 Sterilization

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

**11.8.2** All sterilization processes must be validated. Particular attention should be given when the adopted sterilization method is not in accordance with pharmacopoeial or other national standards or when it is used for a preparation that is not a simple aqueous or oily solution. In any case, the sterilization process must be in accordance with the marketing and manufacturing authorizations.

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

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

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

### 11.8.6 Sterilization by heat

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

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

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

### 11.8.7 Sterilization by moist heat

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

**11.8.7.2** The items to be sterilized, other than products in sealed containers, should be wrapped in a material that allows removal of air and penetration of steam but prevents recontamination after sterilization. All parts of the load should be in

contact with water or saturated steam at the required temperature for the required time.

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

### 11.8.8 Sterilization by dry heat

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

### 11.8.9 Sterilization by radiation

**11.8.9.1** Radiation sterilization is used mainly for the sterilization of heat-sensitive materials and products. Many pharmaceutical products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effects on the products has been confirmed experimentally. Ultraviolet irradiation is not an acceptable method for terminal sterilization.

**11.8.9.2** If radiation sterilization is carried out by an outside contractor, the manufacturer has the responsibility of ensuring that the requirements of section (14.8.9.1) are met, and that the sterilization process is validated. The responsibilities of the radiation plant operator (e.g., for right dose) should also be specified.

**11.8.9.3** During the sterilization procedure the radiation dose should be measured. For this purpose, dosimeters that are independent of dose rate should be used, giving a quantitative measurement of the dose received by the product itself. Dosimeter should be inserted in the load in sufficient number, and close enough together to ensure that there is always a dosimeter in the chamber. Where plastic dosimeters are used, they should be used within the time-limit of their calibration. Dosimeter absorbencies should be read within a short period after exposure to radiation.

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

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

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

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

### 11.8.10 Sterilization by ethylene oxide

**11.8.10.1** Various gases and fumigants may be used for sterilization. Ethylene oxide should be used only when no other method is practicable. During process validation it should be shown that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are such as to reduce any residual gas and reaction products to defined acceptable limits for the type of product or material. These limits should be incorporated into the specifications.

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

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

**11.8.10.4** Each sterilization cycle should be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained should form part of the batch record.

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

**11.8.10.6** For each sterilization cycle, records should be made of the time taken to complete the cycle, of the pressure, temperature and humidity within the chamber during the process, and of the gas concentration. The pressure and temperature should be recorded throughout the cycle on a chart. The record should form part of the batch record.

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

### 11.8.11 Filtration of Pharmaceutical Products that cannot be Sterilized in their Final Container

**11.8.11.1** Whenever possible, products should be sterilized in the final container, preferably by heat sterilization. Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size 0.22 m (or less), or with at least equivalent microorganisms-retaining properties, into a previously sterilized container. Such filters can remove bacteria and molds, but not all viruses or mycoplasmas.

**11.8.11.2** Owing to the potential additional risks of the filtration method as compared with other sterilization processes, a double filter layer or second filtration via a further sterilized microorganism-retaining filter immediately prior to filling may be advisable. the final sterile filtration should be carried out as close as possible to the filling point.

**11.8.11.3** Filters that shed fibers should not be used. The use of asbestos-containing filters should be absolutely excluded.

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

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

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

### 11.8.12 Finishing of Sterile products

**11.8.12.1** Containers should be closed by appropriately validated methods. Samples should be checked for integrity ac-cording to appropriate procedures.

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

**11.8.12.3** Filled containers of parenteral products should be inspected individually. When inspection is done visually, it should be done under suitable and controlled conditions of illumination and background. Operators doing the inspection should pass regular eyesight checks, with spectacles if worn, and be allowed frequent breaks from inspection.

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

### 11.8.13 Quality Control

**11.8.13.1** Samples taken for sterility testing should be representative of the whole of the batch and should in particular include samples taken from parts of the batch considered to be most at risk of contamination, for example:

**a)** For products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant interruption of work.

**b)** For products that have been heat sterilized in their final containers, consideration should be given to taking samples from the potentially cooled part of the load.

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

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

**11.8.13.4** For injectable products, consideration should be given to monitoring the water and the intermediate and finished product for endotoxins, using an established pharmacopoeial method that has been validated for each type of product. For large-volume infusion solutions, such monitoring of water or intermediates should always be done, in addition to any tests required by the marketing authorization on the finished product. When a sample fails a test, the cause of failure should be investigated and remedial action taken where necessary.

# 12. COMPLAINTS

## 12.1 Principle

The drug product quality complaints and reports of adverse reaction should be reviewed by the manufacturer.

**12.2** A system should be established for dealing with complaints.

**12.3** This system should include written procedures indicating the responsible person(s) through whom the complaints are to be channeled. The responsible persons must have appropriate knowledge and experience and the necessary authority to decide the action to be taken.

**12.4** All complaints concerning product quality must be thoroughly investigated. The responsible person should decide whether, and what subsequent action is necessary. This action should be recorded and the record filed with the details of the original complaints.

**12.5** **Complaint record must contain**:

1. Name of the product, batch number, type and origin of the product and complainant.
2. Type and nature of the complaint
3. Details of investigation performed
4. Results of investigation and action taken.

**12.6** Sample of the drug product should be collected and investigated.

**12.7** Complaint records should be regularly reviewed for any indication of a need for recall or of specific problems attention.

# 13. PRODUCT RECALL

## 13.1 Principle

Drug products recall is a procedure which ensures the removing of a drug product promptly and completely from all links of distribution chain.

**13.2** There should be a system to recall products from the market, promptly and effectively at least down to the level of hospitals and pharmacies.

**13.3** A recall can be instituted by government authorities or by the manufacturer.

**13.4** All manufactures must have standard procedure for drug product recall of any batch or lot from the market which is capable of being put into operation at all times. This procedure should contain:

**13.4.1** Degree of recall which should be classified according to the seriousness of the quality defects and adverse reaction of the drug product.

**13.4.2** A responsible person(s) with suitable deputies should be nominated to initiate and coordinate all recall activities. This person should normally be independent of the sales and marketing organization.

**13.4.3.** The method to be used for halting the distribution of the batch or other batches suspected to be subject to an adverse reaction.

**13.4.4** All competent authorities of all countries to which products may have been distributed should be promptly in-formed, if product is intended to be recalled, because it is suspected of being defective.

**13.5 Notification of recall should include:**

**A**. The name of the product, its strength and pack size.
**B**. Batch number.
**C**. Nature of the defect.
**D**. The action to be taken.
**E**. Urgency of the action.

**13.6** The progress and efficacy of the recall process should be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the product.

**13.7** Any recalled products should be placed immediately in quarantine.

## 14. SELF-INSPECTION AND QUALITY AUDITS

### 14.1 Principle

The purpose of self-inspection is to review regularly the manufacturer's compliance with GMP. The self-inspection program should be designed to detect any shortcomings in the implementation GMP and to recommend the necessary corrective actions.

### 14.2 Items for self-inspection

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

**a)** Personnel
**b)** Premises
**c)** Maintenance system
**d)** Storage of starting materials and finished products
**e)** Equipment
**f)** Production and in-process control
**g)** Quality control
**h)** Documentation
**I)** Sanitation and hygiene
**j)** Validation and revalidation
**k)** Calibration of instruments or measurement system
**l)** Recall procedures
**m)**Complaints management
**n)** Labels control
**o)** Results of previous self-inspection and corrective steps taken

### 14.3 Self-inspection team

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

### 14.4 Frequency of self-inspection

The frequency at which self-inspections are conducted depends on company requirements.
Self-inspection can be conducted partially (on production line, facility, sop's...etc.). However, a complete self-inspection should be carried out once a year.

## 14.5 Self-inspection report

A report should be made at the completion of self-inspection and it should include:

**a)** Self-inspection results
**b)** Evaluation and conclusions
**c)** Recommended corrective action

## 14.6 Quality audits

Quality audits consist of an examination and assessment of all or part of a quality system with the specific purpose of improving it. It is usually conducted by outside or independent specialists or a team designated by the management.

# 15. CONTRACT PRODUCTION AND ANALYSIS

## 15.1 Principle

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

## General

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

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

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

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

## The contract giver

**15.6** The contract giver is responsible for assessing the competence of the contract acceptor successfully carrying out the work or tests required and for ensuring by means of the contract that the principle of GMP described in this guide are all followed.

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

**15.8** The contract giver should ensure that all processed products and materials delivered by the contract acceptor comply with their specifications or that the product has been released by the authorized person(s).

## The contract acceptor

**1 5.9** The contract acceptor must have adequate premises, 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 holds a manufacturing authorization.

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

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

## The contract

**15.12** A contract should be drawn up between the contract giver and the contract acceptor that specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis, and GMP. All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

**15.13** The contract should specify the way in which the authorized person releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of the marketing authorization.

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

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

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

# 16-Storage

## 16.1 Principles

Storage facilities for all substances and production components, intermediate products, bulk final products and final products must be made available, and must conform to standards of appropriate storage to avoid contamination, deterioration or spoilage.

Samples are collected and raw materials and production components are measured within the storage facilities, this should be c carried out in areas with standards for control and environmental measures , similar to the standard for production areas for the products in which these materials are used .

## 16.2 General Principles

**16.2.1** Storage facilities and warehouses must be established and equipped to avoid being dirty, contamination , insects and rodents .

**16.2.2** Appropriate standards of safety , control and environmental control must be observed during the storage and handling processes ( including loading and unloading ) in accordance with the conditions and requirements of stored materials and products .

**16.2.3** Appropriate safety standards and environmental criteria must be observed in the storage facilities where flammable materials and drugs that require control are kept .

**16.2.4** Storage facilities must be equipped with equipment for control and registration of temperature and relative humidity, as necessary .

**16.2.5** An automatic alarm system must be installed to alert against adverse environmental circumstances when the occur, together with official written instructions detailing the action that should be taken as soon as the alarm is sounded .

**16.2.6** The Department of specific quality control must be alerted to the changes occurring over the environmental circumstances relevant for storage .

**16.2.7** Official procedures and registers must be available for the following activities and systems :-

a- Environmental supervision and control ;
b- Insect control ;
c- Cleaning and sterilization ;
d- Receiving of materials , elements and products ;
e- Sampling ;
f- Inventory control and circulation , ensuring that the products first in , first out ;
g- Marking products or other alternative procedures to facilitate identifying them ;
h- Applying quarantine procedures on the materials and components that had not been examined as well as procedures for incoming approvals ;
i- Storing rejected and returned substances and components ;

j- Returning materials, components and products from production ;
k- Disposing of rejected and expired materials, components and products .

**16.2.8** A distinctive code must be developed for each consignment , batch of materials, components or products, to help facilitate follow-up .

**16.2.9** In case of absence of consignment code from the supplier, each consignment should be dealt with as a separate one, with respect to sampling, examination and release purposes in the some may as separate consignments of the supplier .

**16.2.10** The procedures for receipt of goods must involve the inspection of all containers to check cleanliness, spoilage , defaults, safety, correctness of codes, comparing the quantities received to those recorded in the purchase request and handing-over documents, etc. Moreover, clear corrective procedures must be defined in case of discrepancies of problems .

**16.2.11** Receipt Registers of materials , products and components must contain the following:-
a-Description of goods .
b- Recording of eye visible defects .
c- Quantities actually received .
d- Name of supplier and recipient body .
e- Consignment number .
f- Date of receipt .

**16.2.12** All containers must be identified by internal identification numbers. Moreover, the consignment number ( if different ) must be attached, together with the container number , the storage conditions , the name of the company , the quality status of the consignment . Alternative methods to identity these data may be used , provided they are as effective and efficient as the above identification system .

**16.2.13** Materials must be stored in shelves or in containers away from the store floors and walls .

**16.2.14** Entry to storage areas of printed packaging materials must be prohibited; and different items and consignments must be well separated .

**16.2.15** Detailed registers of stock release, returning or damage items must be kept to allow follow-up and trace the use of every consignment .

**16.2.16** All sampled containers must be well identified, collected together and released.

**16.2.17** In case of the use of codes to denote quality status, such codes should include the name of the manufacturing company, the description of materials , the code number, the materials and the identification number or the consignment number .

**16.2.18** The stored items earmarked for shipping or distribution or " receipt of request " should be dealt with separately from other materials and products. A system should be available for ensuring the shipping or transfer of approved consignments and parcels .

**16.2.19** Registers of the distribution of finished products must be kept to allow the possibility of following-up and tracing these products to facilitate their withdrawal and retrieval , as necessary .

**16.2.20** The arrangements for the distribution of finished products must conform to the storage conditions recorded on the products card, stating that the product was not subject to any type of damage or contamination .