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GUIDELINES FOR

GOOD MANUFACTURING

PRACTICE

IN EGYPT

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Introduction

Drug products, manufactured locally in Egypt, cover more than 90% of the local consumption. The standards and principles contained in this guide are intended to serve as a reference for the preparation of information on manufacturing practice as requested under the pharmaceutical inspection convention.

This guideline contains the updates of international GMPs for pharmaceuticals with the recommendations of ISO system. Administrative measures of the Egyptian National Health Authority should be directed towards the application of these standards in practice, and any new or amended national regulations for good manufacturing practice should at least meet their level. These standards are also intended to serve manufacturers as a basis for the elaboration of specific rules adapted to their individual needs.

The guide is applicable to all large-scale operations for the production of drugs in their finished dosage forms, including large-scale processes in hospitals and the preparation of clinical trials.

This guide to GMP can be used as a standard to justify GMP status on the Quality of Pharmaceutical Products in Egypt, through the assessment of applications for manufacturing authorizations and as a basis for the inspection of manufacturing facilities.

It may also be used as training material for Egyptian drug inspectors as well as for production and quality control personnel in the industry.

Chapter I

CONCEPTS AND DEFINITIONS

Chapter I: CONCEPTS AND DEFINITIONS

Concepts and Definitions

Active Ingredient A pharmacologically active substance in a pharmaceutical product.

Air Lock An enclosed space with two or more doors only one of which should be opened at any one time and which is interposed between two or more rooms for the purpose of controlling the air flow between them.

Authorized Person A person responsible for the release of batches of finished product for sale.

Batch or Lot A defined quantity of a drug product and/or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.

Batch Number (Lot Number) A distinctive combination of numbers and/or letters, which identifies a batch from which the complete history of the manufacture, processing, packing, holding and distribution of a batch or lot of drug product or other material can be determined.

Batch Numbering System Standard operating procedure describing the details of the batch numbering.

Batch Records All documents associated with the manufacture of a batch of bulk product or finished product which provide a

history of each batch of product and of all circumstances pertinent to the quality of the final product.

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

Calibration The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring, recording, and controlling or the values represented by a material measure, and the corresponding known values of a reference standard.

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.

Consignment (Or 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.

Component Any ingredient intended for use in manufacture of a drug product.

Critical Process A process that may cause variation in the quality of the pharmaceutical product.

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

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

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

Documentation All written procedures, instructions, descriptions, specifications and records involved in the manufacture of a drug product. It is a prime necessity in quality assurance. Its purposes are to define the system of control, to reduce the risk of error inherent in purely oral communication, to insure that personnel are instructed in the details of, and follow, the procedures concerned, and to permit investigation and tracing of defective products.

Drug product A dosage form containing one or more active therapeutic ingredients along with other substances included during the manufacturing process.

Expiration Date The date placed on the immediate container label of a drug product that designates the date through which the product is expected to remain within specifications. If the expiration date includes only a month and year, it is expected that the product will meet specifications through the last day of the month. Kinetically it is the time required for 10% of the material to disappear.

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.

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

Good Manufacturing Practice (GMP(That 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.

in-Process Control Checks performed during production to monitor and if necessary to adjust the process to ensure that the product confirms to its specifications.

ISO (International Standardization Organization) 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.

Types of International Standards on Quality Systems

ISO 9000 For use as a guide to all organizations for quality management purposes.

ISO 9001 For use when conformance to specified requirements is to be assured by the supplier during several stages which

may include design/development, production, installation and servicing.

ISO 9002 For use when conformance to specified requirements is to be assured by the supplier during production and installation.

ISO 9003 For use when conformance to specified requirements is to be assured by the supplier solely at final inspection and test.

ISO 9004 Used together with ISO 9000 as a guide to all organizations for quality management purposes.

Intermediate Product Partly processed material that must undergo further manufacturing steps before it becomes a bulk product.

Inactive Ingredient Any component other than an active ingredient.

Large-Volume Parenterals Sterile solutions for parenteral application with a volume of 100 ml or more 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.

Marketing Authorization (Product License, Registration Certificate) A legal document issued by the competent chug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeia or other recognized specification 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 the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Master Record A document or set of documents that serve as a basis for the batch documentation (Blank Bach Record).

Mean Kinetic Temperature The mean value of the temperature established according to the formula developed by J.D. Haynes. It is a higher value than that of the arithmetic mean temperature. It should be pointed out that the effective or mean kinetic temperature reflects the actual situation better than measured mean temperature, i.e. there is a difference between a product being kept for one month at 20° C and one month at 40° C and two months at 30° C.

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

Packaging All operations including filling and labeling, that a bulk product has to undergo to become a finished product.

Packaging Material Any material, including printed material, employed in the packaging of a pharmaceutical product,

excluding any outer packaging used for transportation or shipment.

Pharmaceutical Product Any medicine intended for human use or veterinary product administered to food producing animals presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in both the exporting state and the importing state.

Process Validation A validated manufacturing process is one which has been proved to do what it purports or is represented to do.

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

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

Quality It is the intrinsic characters of the product which satisfy the user's need.

Quality Assurance Is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

Quality Control 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 the materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

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 by top management.

Utilization Period A period of time during which a reconstituted preparation or the finished dosage form in an opened multi-dose container can be used.

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

Recovery (or Blending) The introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture.

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

Returned Product Finished product sent back to the manufacturer.

Real Time (Long Term Stability Study) Evaluation of experiments for physical, chemical, biological and microbiological characteristics of a drug, during and beyond the expected time of shelf-life and storage of samples at expected storage conditions in the intended market.

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

Standard Operating Procedure (SOP) An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature e.g. equipment operation, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection. Certain SOPs may be used to supplement product-specific master and batch production documentation i.e. it is written instructions describing how to do jobs which could affect product quality.

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

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 dazing, 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.

Shelf-Stability The stability of the drug or drug product at ambient room temperature (15-30° C).

Storage The term used to describe the safe keeping of starting materials, packaging materials, components received, semi finished, in-process and finished products awaiting dispatch. The term also applies for safe keeping of materials and drug products in drug stores, pharmacies, hospitals, etc. under the specified conditions.

Storage Conditions The conditions specified for storing the product e.g. temperature, humidity, container, etc.

Storage Temperatures The actual storage temperature (numerical) used during stability studies.

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

Strength

i. The concentration of the drug substance (for example weight/weight, weight/volume, or unit dose/volume).

ii. The potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, for example, in terms of units by reference to a standard(.

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

Temperature Control All temperatures are in degree Celsius.

a. Cold Place The temperature does not exceed 8.

i. Refrigerator The temperature is thermostatically controlled between 2 and 8.

ii. Freezer The temperature is thermostatically controlled to not higher than -10.

b. Cool Place The temperature is between ٨ and 15.

c. Warm Place Any temperature between 30 and 40.

d. Room Temperature The temperature is between 15 and 30.

e. Excessive Heat Any temperature above 40.

f. Extreme Temperature Fluctuation Cycling through temperature conditions that simulate the changes that may be encountered once the drug product is in distribution.

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

Chapter II

QUALITY MANAGEMENT IN DRUG INDUSTRY

Chapter II: QUALITY MANAGEMENT IN DRUG INDUSTRY

Concept and objective

Quality management is defined as the aspect of management function that determines and implements the quality policy. The quality policy as mentioned in ISO 9000 is the overall intentions and direction of an organization regarding quality, as formally expressed and authorized 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.

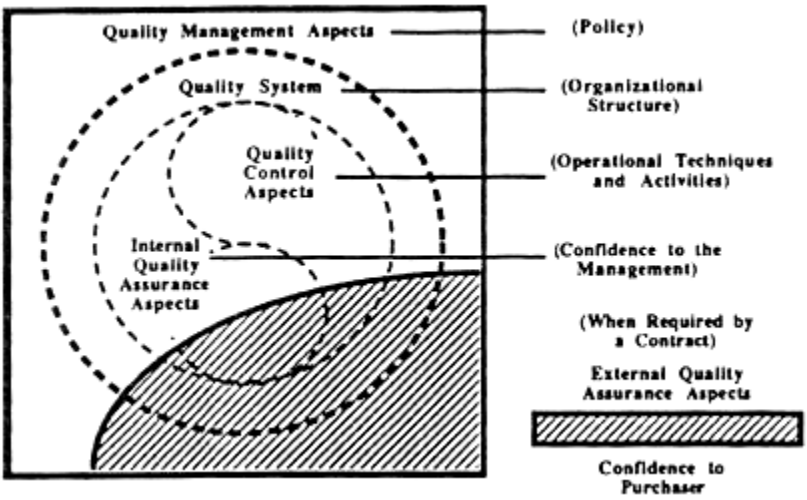
Within an organization, quality assurance serves as a management tool. In contractual situation, quality assurance also serves to generate confidence in the supplier.

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

Quality must be built into a drug product during product and process design, and it is influenced by the physical plant design, space, ventilation, cleanliness, and sanitation during routine production.

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

- The relationship of the different concepts are shown in Figure (1)



1. *Activities aimed at providing confidence to the management of an organization that the intended quality is being achieved are often called internal quality assurance.*
2. *Activities aimed a providing confidence to the purchaser that the supplier's quality system will provide a product or service that will satisfy the purchaser's stated quality requirements are often called external quality assurance.*

Fig. (1) Relationship of Concepts

Quality assurance

Concept and objective

Quality assurance is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the quality required for their intended use.

Quality is not an accident, it has to be planned, quality can not be tested in the final product, it must be designed and built in.

Quality must not be confined to compliance with specification, it requires adoption of wide view of quality. Highest quality is customer full satisfaction. Manufacturing and marketing of safe effective products of the highest quality is the main objective of quality assurance.

Quality assurance therefore, incorporate both GMP, quality control and other factors such as product design a development.

The organization of a quality assurance system

The organization of a quality assurance system may vary according to the structure of an individual company, but it should incorporate certain basic features e.g.

a. A quality policy which defines the purpose and objectives of the organization and outlines the ways in which these will be achieved.

b. Resources, including personnel, equipment, facilities, finance, materials and technical skills.

c. Documentation, including procedures, standards and methods.

d. An audit process to assure proper adherence to the defined procedures and to provide a mechanism for improving the quality system itself.

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

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

b. Production and control operations are clearly specified in a written form.

c. Managerial responsibilities are clearly specified in job descriptions.

d. Arrangements are made for the manufacture, supply, and use of the correct starting and packaging materials.

e. All necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out.

f. The finished product is correctly processed and checked, according to the defined procedures.

g. Pharmaceutical products are not sold or supplied before the authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other

regulations relevant to the production, control and release of pharmaceutical products.

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

i. There is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system.

Responsibility of the quality assurance officer

The responsibilities of the quality assurance officer can be summarized as follows

1. Sampler To obtain representative samples of intermediates and finished product

a. For each batch.

b. According to the specification.

c. As required to meet special needs e.g. process problems.

2. Checker To perform independently in-process quality control (checks and tests)

a. At random throughout process.

b. For critical start-up tests.

c. To check for correctness of printed materials and overprinted items.

3. Observer To observe conditions on line and in process area

a. For compliance with the process method.

b. For correct operation of procedures.

c. For cleanliness, and clearance of other components.

4. Reporter To prepare a batch report on

a. The key components used and their status.

b. Clearance and cleanliness.

c. In-process checks.

d. General comments on conditions in the area and flow of process e.g. machine stoppage and actions taken.

5. Reviewer To review the manufacturing/packaging record for

a. Completeness.

b. Correctness.

c. Compliance of in-process control results with specification.

d. Reporting of "unusual incidents".

Quality control

Concept and objective

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

quality has been judged to be satisfactory. Quality control as mentioned in ISO 9000 is the operational techniques and activities that are used to fulfill requirements for quality.

Provision for a cross referencing system to allow any batch of a product to be traced from its raw materials to its final destination in the event of unexpected difficulties is required.

In order to avoid confusion, care should be taken to include a modifying term when referring to a sub-set of quality control, such as manufacturing quality control, or when referring to a broader concept, such as company-wide quality control.

Quality control involves operational techniques and activities aimed both at monitoring a process and at eliminating causes of unsatisfactory performance at relevant stages of the quality loop (quality spiral) in order to result in economic effectiveness.

To achieve effective control of quality the follow in should be taken in consideration

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

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

c. Test methods must be validated.

d. Records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting, and resting procedures have actually been carried out and that any deviations have been fully recorded and investigated.

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

f. Records must be made of the results of inspecting and testing materials and intermediate, bulk, and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures.

g. No batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the requirements of the marketing authorization.

h. Sufficient samples of starting materials and products must be retained to permit future examination of the product if necessary; the retained product must be kept in its final pack unless the pack is exceptionally large.

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

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

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

In-Process quality control

To guarantee the manufacturing symmetry, controlling tests should be carried out on certain samples at each production step. Approved production steps should be controlled and assured for example

- Variation in weight for any pharmaceutical product.
- Disintegration of tablets.
- Assurance of mixing to verify homogeneity for powders.

- Dissolution rate for certain solid dosage form.
- Volume, pH, clarity tests for solutions.
- Appropriate tests for semisolids, or sterile products.

These tests must comply with the final requirements of products. If the raw material is kept in the store for long period, controlling tests during manufacturing must be carried out for assurance of its purity and validity. Raw materials do not pass these controlling tests must be quarantined, identified by special labels, not be used and be returned to the quarantine store for damage under concerning committee supervision.

Sampling

All raw materials, packaging materials, containers should be kept in the quarantine area until sampled by quality control and approval result is issued. No batch is used until all tests are approved by quality control.

Any batch that does not conform to standards should be rejected. All tests should be changed according to the latest pharmacopoeia and its addendum and other advanced text books and the most recent modification devised by factory.

The samples should cover a certain part of the batch, with a written procedure and fixed plan. Sampling should be taken without causing any contamination to the containers.

Sampling Procedure Should Include

- How to take the sample.

- The equipment used for sampling.
- Quantity to be sampled.
- Instructions for how to divide the sample.
- Care should be taken for the cleanliness of the sampling container especially for sterilized materials, and highly effective materials.

The sampling container should be labeled with the following requirements

- Material name.
- Batch no.
- The container no. which is sampled.
- Name and signature of the sampler.
- Date of sampling.

Tests for samples

Raw materials Each material should be tested according to the specification specially physical properties (including particle size, crystal shape, hydrated form) purity, content identification and others including content of degradation products. Quality control results are the only accepted ones.

Intermediate containers and large volumes All specifications of tests specially identification, purity, homogeneity in mixing and other tests.

Large volume containers Tests may include weighing variance, disintegration rate, dissolution rate for tablets and capsules, clarity, volume, pH for solutions, homogeneity in content and sterility rests (if needed).

All batches that are not accepted from quality control results are rejected and take a different label color indicating that it is rejected except if it require reworking.

Each product should have its up-to-date specifications, and tests to be done on each batch before release.

No release is issued for batches that does not confirm with any specification. It is rejected or remanufactured and requested for quality control to be released or rejected.

Sterile products should be tested for sterility. This test does not assure the sterility of the whole batch, because it is a random sample and the contaminated products are not sampled or the sensitivity of the test method does not permit the growth of microorganism so precautions have to be done.

Samples should be taken randomly from the coldest sterilization place and samples from start and end of sterilization. Samples are taken as a percentage of batch quantity, and tests are made for aerobic and anaerobic bacteria.

Media for test should be chosen to permit the growth of microorganism at any number. Media should be sterile. If a batch failed, the test should be validated. The results should be recorded, for future knowledge of the reason for the test failure, or method of preparation.

Pyrogen test (coming from raw materials, personnel, equipment or environment on long preparation time) needs a big attention for large volume products for

- Water should be pyrogen free specially for volumes more than 15 ml
- On the preparation of large volume parenteral all precautions should be made to avoid the formation of pyrogen.
- All parentral solutions that are more than 10 ml. should be free from pyrogen.

Quality control release system

In defining the overall system for quality control release of finished products, it is for the manufacturing organization to decide on

- The timing of the review of batch documents and analytical results
- The extent to which batch data are used to authorize further processing of intermediates and pan finished products.

The two most convenient ways of doing this are

- To review batch documents/analytical data on completion of each manufacturing stage and release finished product on the basis of finished pack "inspection" and confirmation that earlier stages have been previously approved.

- To sample finished packs for full analytical testing and carry out the batch document evaluation and finished pack inspection on completion of packaging.

Whatever system is chosen, quality control release of finished products will depend on the availability of satisfactory

- Bulk manufacturing records (e.g. Granulation).
- Intermediate processing records (e.g. tablet compression).
- Packaging records.
- Records of in-process checks (the majority of these normally appear in the production records).
- Reconciliations of product and material usage at each stage of the process and evaluation of the yield for the manufacturing process overall.
- Reports giving analytical and/or microbiological results.
- Requests for release/transfer/shipping of the batch.

In practice it may be convenient to use checklists for each product category or activity which ensure and record that all the necessary documents and results have been gathered together, reviewed, checked, assessed as satisfactory and filed. The checklist should be filed with the batch records and the document or copy document authorizing the disposition of the batch.

The batch documentation or a suitable summary should be submitted to a person authorized to carry out quality control release who should then satisfy him/herself that all the documents detailed

above have been duly completed and checked, and any exceptions investigated and reported.

Where checks reveal deviations from accepted practices, unforeseen events or analytical results outside "release" limits, the person legally responsible for quality control and the appropriate "qualified person" must agree the fate of the batch concerned. In these circumstances, the following factors should be taken into account

- The requirements of the product license and manufacturer's license.
- The stability of the product and the end of life (check) specification for the product.
- The results of investigations carried out into the history of the batch

On completion of all the necessary checks, the person authorized to carry out quality control release should sign for the disposition of the batch in the formal records. If this person is also carrying out the duties of the "qualified person" he or she will need to ensure that additional checks are carried out as appropriate and that the batch is entered on the register which is then signed. Where a second person is carrying out the duties of the "qualified person" quality control must ensure that he or she is provided with sufficient information to carry out his/her duties and that each batch has been signed off in the register.

Once all these checks and the batch certification are completed, the person responsible for quality control release can sign the documents that authorize transfer to stock or shipping.

Checklist for premises

for quality assurance, production, process and laboratory controls

Facilities	***Status***
General cleanliness of area	
No leaks, holes, cracks in building/windows	
No insects/rodents/vermin	
No unrelated traffic/pedestrian flow	
Area secured behind closed doors	
Floors/walls covered with material to facilitate cleaning	
Size of facility adequate	
Separate area for	
- QC/QA for	
- Raw materials	
- Mixing/blending intermediates	
- Finished dosage forms	
- QC/QA , tests that are performed	
- Animal receipt/holding/testing	
- Special storage for special requirements	
Necessary utilities in sufficient quality and quantity	
Adequate lighting and Ventilation	

Checklist for personnel

working in quality assurance, production, process and laboratory controls

Personnel	***Status***
Determine minimum number of personnel needed	
Position Description (PD) for each employee	
Chart key functions/personnel	
Identify basic qualification for each PD	
Identify special skills for each PD	
Identify key staff and delegate / assign responsibilities needed for proper functioning e.g. supervising / training / maintenance	
Develop training program	
Schedule periodic retraining	
Schedule periodic performance evaluations	

Checklist for equipment

of quality assurance, production, process and laboratory controls

Equipment	***Status***
Dedicated equipment and instruments available for	
Special storage constant room temperature and humidity	
Measuring/weighing/sampling	
Laboratory for all assays and tests conducted	
Cleaning equipment	
Sealable containers for storage of materials to be tested	
Equipment in good working order	
Cleanliness	
Maintenance/lubrication according to schedule	
Calibration	
Validation	
Correct equipment available	
Equipment/supplies/ available to lubricate, calibrate, maintain, and repair	

Chapter III

PERSONNEL

Chapter III: PERSONNEL

Concept and objective

There should be sufficient personnel at all levels with the ability, training, experience and, where necessary, the professional/technical qualifications and managerial skills appropriate to the tasks assigned to them. Their duties and responsibilities should be clearly explained to them and recorded as written job descriptions or by other suitable means. Training should cover not only specific tasks but Good Manufacturing Practice generally and the importance of personal hygiene.

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

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

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

Key personnel

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

Key personnel responsible for supervising the manufacture and quality control of pharmaceutical products should possess the qualifications of a scientific education and practical experience required by national legislation. Their education should include the study of an appropriate combination of (a) chemistry (analytical or organic) or biochemistry, (b) chemical engineering, (c) microbiology, (d) pharmaceutical sciences and technology, (e) pharmacology and toxicology, (f) physiology, or (g) other related sciences. They should also have adequate practical experience in the manufacture and quality assurance of pharmaceutical products. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of experts should be such that enable them to exercise independent professional guidance, based on the application of scientific principles and understanding of the practical problems encountered in the manufacture and quality control of pharmaceutical products.

Personnel responsibilities

Factory Manager (FM)

FM must be a pharmacist, registered in Ministry of Health, has experience in pharmaceutical manufacturing not less than 15 years. He (she) receives the reports from the different sectors' chiefs, put the general present and future plans for manufacturing. He (she) helps in selecting the supervisors.

Production Sector Chief (PSC)

PSC must be a pharmacist registered in ministry of health, has experience in pharmaceutical manufacturing not less than 10 years. He (she) generally has the following responsibilities

a. To ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality.

b. To approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation.

c. To ensure that the product records are evaluated and signed by a designated person before they are made available to the quality control department.

d. To check the maintenance of the quality production departments, premises, and equipment.

e. To ensure that the appropriate process validation and calibrations of control equipment are performed and recorded and the reports made available.

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

Quality Control Sector Chief (OCSC)

QCSC must be a pharmacist, registered in Ministry of Health, has experience in quality control not less than 10 years. He (she) generally has the following responsibilities

a. To approve or reject starting materials, packaging materials, and intermediate, bulk, and finished products.

b. To evaluate batch records.

c. To ensure that all necessary testing is carried out.

d. To approve sampling instructions, specifications, test methods, and other quality control procedures.

e. To approve and monitor analyses carried out under contract.

f. To check the maintenance of the quality production departments, premises and equipment.

g. To ensure that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are done.

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

Sectors Supervisors (SS)

In the manufacturing, quality control, and others, sectors supervisors should be with high professional levels according to their responsibilities. They give reports to the sector chiefs.

Consultant

Consultant should be with special high level of scientific and experience background. The work of any consultant should be continuously reported.

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

a. The authorization of written procedures and other documents including amendments.

b. The monitoring and control of the manufacturing environment.

c. Plant hygiene.

d. Process validation and calibration of analytical apparatus.

e. Training, including the application and principles of quality assurance.

f. The approval and monitoring of suppliers of materials.

g. The approval and monitoring of contract manufacturer.

h. The designation and monitoring of storage conditions for materials and product.

i. The retention of records.

j. The monitoring of compliance with GMP requirements.

k. The inspection, investigation, and taking of samples, in order to monitor factors that may affect product quality

l. Follow up of the product recall and dealing with complaints.

Personal Hygiene The importance of personal cleanliness, washing of hands, and general personal hygiene should be emphasized.

Personal Health Pre-employment and periodic medical checks should be required and staff should be encouraged to report any infections, disease, skin lesions or any condition that may endanger product quality. Management should develop procedures as to actions to be taken in the event of an infection being observed among workers.

Training

The first need in developing national competence in drug control is the training of key staff in every aspect of regulation and enforcement. It is recognized that international coordination of training programs and of the production of educational material is essential to success.

Besides basic training on the practice of GMP, newly recruited personnel should receive training appropriate to the duties

assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programs should be available, approved by the head of either production or quality control, as appropriate, training records should be kept.

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

Priority, if suggested, should be according to the following elements

- Budgeting for and management of quality control laboratories.
- Training of laboratory technicians.
- Maintenance of equipment.
- Training on new technology in drug production.
- Promotion of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce.
- The concept of quality assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

Chapter IV

PREMISES

Chapter IV: PREMISES

Concept and objective

Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and in general, any adverse effect on the quality of products. Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

Premises used for the manufacture of drug products should be suitably designed and constructed to facilitate good sanitation. Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products. Premises should be cleaned and, where applicable, disinfected according to detailed written procedures.

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

There should be air filtration devices which have the ability to change the air at suitable rate for each area. For each area number of particulate matter must be identified according to special specifications related to each area.

There should be water source under continuously high pressure in the water which must be of suitable capacity to prevent any defect. Tanks must not allow the loss or contamination of water. There should be unit for removal of large particles, microbes and hardness from the water. System used for preparing sterile water requires continuous validation.

The factory should contain areas for

- Receiving the raw materials, packages and others. These receiving areas should be separated according to the size of each item.
- Raw materials store.
- Rejected raw materials, final products and labels.
- Central dispensing for general weighing and preparation. This area must be separated according to the type of ingredients. Laminar flow is a must for weighing materials used for sterile product.
- Manufacturing area.
- Packaging area.
- Quarantine area for product under testing for their release.
- In process quality control room inside production.
- Quality control department.
- Sterile area needs
    - Washing area.

- Mixing area.
- Filling and sealing area.
- Closed area adjacent to the filling.
- Dressing room for sterile area.
- Sterile area.

Construction and finishes

Construction must be adequate to minimize the entry or harboring of insects, birds or rodents and have smooth, robust, non-porous, easy to clean and easily maintained surfaces, free from cracks, crevices and ledges.

Finishes in processing areas should not shed or harbor particulates or absorb micro-organisms. Parameters such as porosity, density, texture and electrostatic properties must be considered. The use of wood should be avoided in production and packaging areas. Where present, it should be adequately sealed with emphasis on flexible coating to minimize chipping.

The type of material and finish used for floors, walls and ceilings cannot be considered in isolation as in many instances the same or similar materials are used. The compatibility of the different materials used must be considered together with the junctions between them.

i. Floors and walls

Floors should be hard, smooth, sealed, impervious, laid to an even surface and not affected by cleaning materials. For clean and

aseptic areas higher standards are appropriate. Expansion joints and cracks, if present, should be sealed with a suitable resilient compound flush with the surrounding surfaces.

Floors and walls must be sealed to render them impervious to penetration by materials processed in the area. Defects in the floor and wall surfaces which could admit and harbor materials processed in the area, dirt, insects, birds, rodents and debris should be repaired. Where necessary, floors should be adequately sloped towards floor drains to prevent accumulation of washings and spillages.

Joints between walls and floors should be easy to clean, adequately sealed and preferably coved. Any piping, ducting or other structural materials passing through walls must be sealed at point of entry to prevent contamination by dust and debris of products processed below.

ii. Ceilings

Ceilings should be constructed and finished so that they are easy to clean. The ceiling surface must be well maintained and free from peeling or other visible deterioration. If ceiling tiles are used they must fit securely into position, have a smooth surface and be adequately sealed to prevent contamination from the space above them.

The joint of the ceiling with the wall should be complete and preferably coved. Any piping, ducting or other structural materials passing through the ceiling must be sealed at point of entry to

prevent contamination by dust and debris of products processed below.

Overhead ducts, roof joists, pipes and lighting fixtures should be avoided in the manufacturing and packaging areas since they are not readily cleanable surfaces. They should be contained within a suspended ceiling to reduce surfaces where dust can accumulate and access for maintenance must be clearly identified. Where the ceiling consists of the floor of an area above, it should incorporate a damp proof membrane to prevent seepage.

iii. Doors and windows

Doors and windows should have a smooth, hard, impervious finish and should close tightly. Window and door frames should be flush with the surrounding walls. Windows, if present in the production area, should be tightly sealed and not be permitted to open.

Outside doors should be well sealed and be closed except when used for entry or exit. Inside doors used to segregate operations to prevent cross contamination must be closed except when used for entry or exit. Doors which lead to the outside directly from production areas should be absolutely sealed and closures designed such that they can only be used as emergency exits. Sliding doors are a potential problem if they cannot be cleaned easily. A major advantage however is the extra space that such doors provide.

Consideration must be given to the potential conflict of Good Pharmaceutical Manufacturing Practice (GPMP) and fire, health and safety requirements.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Floors							
▪ High-density concrete	x	x	x	x	x	x	x
▪ Troweled epoxy finish	x	x	x		x		
▪ Terrazzo epoxy finish	x	x	x		x		
▪ Concrete with metal chips drains	x	x	x	x	x	x	x
▪ Vinyl asbestos tile	x		x	x		x	x
Walls							
▪ Smooth	x	x	x	x	x	x	x
▪ Epoxy paint	x	x	x	x	x	x	x
▪ Washable	x	x	x	x	x	x	x
▪ Glazed tile	x	x	x	x	x	x	
▪ Wall paper (washable)			x			x	
Ceilings							
▪ Hung	x	x	x	x	x	x	
▪ Acoustical	x		x	x	x	x	
▪ Smooth waterproof		x					
▪ Open							x
Lighting							
▪ Foot candles	75	100	100	75	75	75	50
▪ Flush mounted	x	x	x	x	x	x	
Air conditioning							
▪ Optional		x			x		
▪ Comfort control		x			x	x	
▪ 45% RH/22.2° C	x		x	x			
▪ <20% RH/22.2° C			x				

(1) = Chemical Weighing
(2) = Granulating
(3) = Tabletting
(4) = Coating
(5) = Liquid manufacture
(6) = Packaging
(7) = Ware-housing

Table (1) Facilities Guidelines

Environment

Microbial and particulate quality is especially important in the manufacture of sterile and many oral and topical products. It is necessary to monitor production areas regularly for the absence of micro organisms and for particulate levels as appropriate to ensure that the environment is satisfactory for manufacturing.

a. Requirements for specific manufacturing areas

i. Sterile areas

The requirements for a clean and correct environment in sterile areas are most stringent because most products manufactured therein are for direct injection into the body thus avoiding some of the normal body defense mechanisms. Other products manufactured in sterile area such as eye, nose and ear medicines are applied to sensitive areas. The prevention of contamination by particles and micro-organisms is, therefore, important, and the way of preventing this contamination is to control carefully the environment in which they are manufactured. There are other environmental factors which can affect sterile products including humidity and temperature. These are normally product specific and need to be considered as special cases.

Contamination of a sterile area environment by particles and micro-organisms can normally be considered together when discussing the methods of producing a satisfactory aseptic environment but have to be considered separately in terms of monitoring methods. Sterile areas should normally be flushed with at least 20 air changes per hour, the air having passed through "High

Efficiency Sub-micron Particulate Air" (HESPA) filters. The air flow is arranged to pass over the most critical areas before exhaustion or recirculation. HESPA filter integrity checks should be conducted on a regular basis. Clean room conditions are maintained by providing positive pressure to reduce ingress of particles and micro-organisms from surrounding areas. The temperature of the filtered air controls the temperature of the sterile area. Very often the humidity of the air is also controlled simultaneously in order to provide a comfortable environment for the operators, who should be clad in non-particle shedding clothing to minimize their contribution of particles to the atmosphere. Localized laminar flow protection may be necessary if the entire area cannot be ventilated to an acceptable standard.

Particulate contamination is normally measured using light scattering instruments such as the Royco counter. This instrument draws air into a chamber where the number and size of particles is determined. The results of these counts need careful interpretation in the context of the operations being carried out and the accuracy of the determinations. Output from these instruments is normally by means of a digital display or printed chart, but may be connected to a loudspeaker to give an audible count. This latter output is useful for giving an immediate indication of leaks when inspecting filter surfaces. Care is necessary to ensure that standard procedures are available for particle counters including locations and times of tests.

Detection of viable micro-organisms in the air can be carried out by two methods. The first includes the use of centrifugal or slit type samplers which collect a measured volume of air and direct it over solid nutrient medium in the form of a plate or strip so that the

microorganisms impinge on it and can grow colonies on subsequent incubation. These colonies can be counted and related to the volume of air sampled. The second method relies on the exposure of settle plates in various areas of the production suite. One advantage of this technique is that it is easier to cover more of the area for more of the time, but it has the drawback of needing much background data before limits can be applied as the response (collection of viable micro-organisms) relies on air currents, settling rate of particles, time of exposure, etc. Contact plates may also be used in conjunction with settle plates. A formal and agreed testing regimen with defined action should be drawn up and agreed.

ii. Liquids, creams, and ointments manufacturing

The environment for the manufacture of these products does not need to be the same as for sterile products but, because they need to be manufactured in an environment from which significant microbial contamination is excluded. Particular care is required with the environment for creams and ointments as such products may be used on abraded skin surfaces.

It is preferable that this environment is at positive pressure relative to the surrounding area and that it is kept clean and the facility adequately disinfected. The air supply should ideally be filtered to remove particles which could contaminate the product or harbor micro-organisms.

iii. Solid dose area

The major contamination of the environment in solid dose areas arises from the product itself, although care must also be

taken to minimize the microbial exposure. Environmental conditions must also be maintained to protect the operator in these areas because dust of any nature is potentially harmful to the lungs, and active dust could have physiological effects on the operator.

Control of the environment in these areas is normally achieved by directing the filtered ventilation air across the product towards the extract and away from the operator position. There should also be localized dust extraction for certain operations such as milling. No amount of ventilation and dust extraction can substitute the prevention of dust generation. This must be the prime aim in achieving a clean environment. Tabletting areas also need to have humidity control for many types of products such as effervescent tablets and this is achieved by controlling the input air.

Measurement of dust is normally achieved by drawing air through a suitable cellulose or glass fiber filter and collecting and weighing the dust. Static monitors are useful for measuring the dust created by a machine or an operation, whereas personal monitors indicate the exposure of the operator to a potential hazard. Tests could be performed on operators to determine the concentration of active ingredients in their blood or urine samples.

iv. Dispensary

Dispensing areas are similar to solid dose areas and care needs to be taken to control dust generation whilst transferring material. The design of the ventilation and dust extraction equipment needs to keep dust away from the operator and at the same time not

cause contamination of other products. Measurement of dust in dispensing areas is by the same methods as for solid dose areas.

b. Dust and dust extraction

Dust, if it contaminates other products, may be a risk to a patient's health. It may also harm the personnel working in a manufacturing area by blocking nasal passages, causing accidents due to the effect of the drug on the person or even inducing diseases in the lungs.

There is a conflict between the GPMP and the health and safety approach to dust control and prevention. The former requires the product to be protected and could, therefore, mean that clean air is directed at the product (and then over the operator), whereas the latter requires the clean air to pass over the operator first. In fact, these two views can largely be reconciled by using correct protective clothing 'for the operator and minimizing dust generation using closed vessels where possible and adequate dust extraction. Certain hazard cabinets can protect both the operator and the final product.

The presence of dust in the atmosphere is restricted where limits of less than 10 mg/cubic meter of air are applied.

c. Lighting

Without adequate lighting, personnel cannot carry out their work satisfactorily. Too little light causes eye strain and fatigue, especially where detailed work is performed, whereas too much light can cause glare and dazzle. Where possible, daylight is preferable to any artificial lighting because the human eye is more accustomed to

the color balance of normal daylight. Some substances are, however, sensitive to UV radiation present in daylight.

Not all rooms can be lit completely by daylight and artificial lighting is widely used. Due consideration must then be given to positioning, color balance and intensity. Domestic fluorescent tubes give an emission spectrum which is deficient in certain colors and daylight tubes should be selected where possible (see table1)

d. Noise

Noise is part of the environment and can affect personnel severely once a threshold level of 90 dB has been reached - a maximum of 80 dB should be the objective. It is difficult to define because the frequency of noise volume and the annoyance it causes are not related. Certain frequencies and combinations of frequencies at a low level can be more irritating than other combinations.

e. Color and decoration

Companies often use a common color scheme for decoration throughout a factory which means that the environment may have a monotonous appearance. Careful choice of decoration color can enhance the working environment.

Requirements of different areas

i. Ancillary areas

Rest and refreshment rooms should be separate from other areas. Facilities for changing and storing clothes and for washing and toilet purposes should be accessible and appropriate for the

number of users. Maintenance workshops should if possible be separated from production areas.

Animal houses should be well isolated from other areas, with separate entrance and air handling facilities.

ii. Storage area

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

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

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

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

There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it

should be conducted in such a way as to prevent contamination or cross-contamination.

Segregation should be provided for the storage of rejected, recalled, or returned materials or products. Highly active materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire, or explosion should be stored in safe and secure areas.

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

iii. Weighing areas

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

iv. Production areas

In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g. penicillin) or biological preparations (e.g. life microorganisms). The production of certain other products, such as some antibiotics, hormones, cytotoxic substances, highly active pharmaceutical products, and non-pharmaceutical products, should not be conducted in the same facilities. The manufacture of technical poisons, such as pesticides,

and herbicides should not normally be allowed in premises used for the manufacture of pharmaceutical products. In exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made.

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

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

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

Pipe work, light fittings, ventilation points, and other services should be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas. Drains should be of adequate size and equipped to prevent back-flow. Open channels should be avoided where possible, but if they

are necessary they should be shallow to facilitate cleaning and disinfection.

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

Premises for the packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination. Production areas should be well lit, particularly where visual on-line controls are carried out.

v. Quality control area

Quality control area laboratories should be separated from production areas. Areas where biological, microbiological, or radioisotope test methods are employed should be separated from each other. Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), and records.

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

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

Cleaning of the building

All production units, packaging and others should be always clean and in the adequate maintenance. There should be written procedure for cleaning of all sectors with clear insurance of cleaning responsibility with identified and fixed steps for cleaning. The rubbish and the manufacturing remainders should be removed as soon as they are collected. Equipment, raw materials and pharmaceutical products should not be contaminated by pesticides and rodenticides. Workers uniform should be kept in special lockers. There should be special places for eating, drinking and smoking. It should be left clean and controlled. There should be places for water closets and dressing units in separated areas from the manufacturing and control areas. Separation is achieved by doors and positive pressure.

Personnel in the manufacturing and the other areas and all workers should practice the different hygienic methods by the written methods with attention if they didn't obey. All workers should keep their dressings and their bodies clean. Unclean clothes are kept in special places. All workers must be subjected to periodical medical check up to protect the pharmaceutical products from contamination with germs. In case where possibility of workers contamination, check up for liver and kidney functions are required. Persons who work in the sterile sections should be subjected to periodical medical check up. All efforts must be carried to prevent contact between the

workers and the raw materials or packaging materials. Teaching the workers how to wash their hands before entering the manufacturing areas is essential with unknown marks if possible to test if they didn't obey.

Chapter V

MATERIALS

Concept and objective

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

Raw materials

The main requirements for raw materials used in pharmaceutical processing are that

- Adequate systems exist to ensure that all raw materials are purchased from approved sources and also that, prior to use, each batch is approved by quality control as conforming to the specifications.
- They are properly labeled with the name, code number and expiry and retest dales.
- Their quality control status is evident either from a label or an equivalent system.
- They are stored under conditions which prevent unacceptable changes.

The elements of purchasing and inventory control policy that affect the quality of raw materials and products should be approved by the person responsible for quality control and should be stated formally. Materials should be ordered, taken from stock (normally on a first-in first-out basis) and supplied to processing units in

accordance with formally approved procedures which should include checks to ensure that

- The correct material, grade, amount and batches are ordered, drawn from stock and delivered.
- Each container is correctly labeled with the amount contained, identity, batch and code numbers and, if necessary, the quality status of its contents (where labeling does not include quality status this should be confirmed by alternative means).

Checks should also be carried out to ensure that containers are externally clean and in a satisfactory condition. If not, they should be cleaned on entry into production or measuring-out areas.

All transfers of material and associated checks should be recorded in formal documents which permit the details of the transaction to be traced and checked retrospectively. All transfers should be recorded in terms of

- Quantities
- Dates
- Personnel involved
- Batch numbers
- Materials code numbers
- Quality control status

Records should also permit reconciliation procedures to be carried out in order to verify that the correct amounts have been used.

Where materials are transferred from suppliers' containers to special in-house ones, all the relevant information must be transferred from the original to the new container, with a recorded check being carried out to ensure that this has been done correctly.

When raw materials are being allocated to individual batch of product, care must be taken to avoid the inclusion of too many batches of any one item as later this can pose problems with batch traceability and the investigation of problems.

Raw materials are liable to deterioration during storage and, as a consequence, should normally be given a "retest" date when they are approved for use by quality control. This information should be carried forward into production to ensure that any materials stored there, are not used after the specified date without having first being retested.

Where production planning policies and practices influence the quality of finished products, they should be approved by the person responsible for quality control and should be staled formally.

Where raw materials are handled for products which have a microbiological specification, special procedures and monitoring may be necessary. These may include disinfection of equipment and areas, use of special protective clothing and procedures together with microbiological monitoring.

Packing materials

Special characteristics should be put for all packaging materials.

- Every package batch should be inspected

- Every printed package should be kept in the quarantine till pass through special tests carried out by quality control responsible persons.
- Packages which are affected by humidity should be kept in suitable conditions to protect them.
- Package kept in papery boxes should not be kept on the floor.
- Outdated or obsolete primary packaging materials or printed packaging material should be destroyed under strict security controls and its disposal recorded.

Intermediate and bulk products

Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials and should be kept under appropriate storage conditions.

Finished products

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

Rejected and recovered materials

Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed.

The reprocessing of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record should be kept of the reprocessing. A reprocessed batch should be given a new batch number. The need for additional testing of any finished product that has been reprocessed, or into which a recovered product has been incorporated, should be considered by the quality control department.

Recalled products

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

Returned goods

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

Reagents and culture media

All reagents and culture media should be recorded upon receipt or preparation. Reagents made up in the laboratory should be prepared according to written procedures and appropriately labeled. The label should indicate the concentration, standardization factor, shelf-life, the date when re-standardization is due, and the storage conditions. The label should be dated and signed by the person preparing the reagent.

Reference standards

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

Waste materials

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

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

Gases

Gases include a wide range of active and inert gases used in various stages of pharmaceutical manufacture and laboratory testing and may be categorized as those gases which come into contact with the pharmaceutical product or container. These should be treated as normal raw materials, and be subjected to standard testing and release procedures. Filtration should occur, preferably at the point of use. Control is also necessary with gases of which the quality may influence the results of laboratory testing of products.

Where possible, an identity test (as a minimum) should be conducted on each cylinder to prevent the use of incorrectly filled cylinders. Since this is not always feasible, a high level of supplier assurance should be obtained by detailed auditing of the supplier's facilities and procedures. For cylinder gases, particular attention must be paid to the batching, filling, segregation from other gases, procedures to avoid cross-connecting of pipe-work, and care of cylinders. The frequency of checking, and cleaning of both cylinder and valve system, is of particular significance.

All cylinders should be correctly color-coded according to the required standards, and be marked with a unique identifying mark, ideally at the shoulder to allow traceability of individual cylinders in use.

Cylinders should be stored under cover, and not subjected to extremes of temperature. Areas where they are stored should be clean, dry, well ventilated and free from combustible materials. Pressure gauges should be checked frequently and re-calibrated regularly against a primary standard.

Solvents

Solvents which are used in any pharmaceutical manufacturing process should be considered as raw materials, regardless of whether they remain in the finished product or are removed during processing. The solvent is properly identified and assayed, before permission is given to unload the material. To avoid potential safety risks, the identity test chosen must be as specific as possible for the solvent.

Whenever possible, a certificate of analysis from the supplier should accompany each consignment. Strict written procedures should be followed to ensure the receipt, testing and quality control release.

Miscellaneous

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

Checklist for premises of raw materials

Facilities	***Status***
General cleanliness of area	
No leaks, holes, cracks in building/windows	
No insects/rodents/vermin	
No unrelated traffic/pedestrian flow	
Area secured behind closed doors	
Size of facility adequate	
Separate areas for Quarantine.	
Testing and evaluation.	
Weighing.	
Storage of approved materials.	
Special storage for special requirements.	
Necessary utilities in sufficient quality and quantity.	
Adequate lighting and ventilation.	

Checklist for personnel working in raw materials

Personnel	***Status***
Determine minimum number of personnel needed	
Position Description (P.D) for each employee	
Chart key functions/personnel	
Identify basic qualification for each P.D.	
Identify special skills for each P.D.	
Identify key staff and delegate/assign responsibilities needed for proper functioning e.g. supervising /training / maintenance.	
Develop training program	
Schedule periodic retraining	
Schedule periodic performance evaluations	

Checklist for equipment of raw materials

Equipment	***Status***
Dedicated equipment available for	
Lifting and transporting	
Special storage-constant room temperature	
Measuring/weighing/sampling	
Laboratory testing	
Cleaning equipment	
Sealed containers available for transfer to mixing area	
Equipment in good working order	
Cleanliness	
Maintenance/lubrication according to schedule.	
Calibration	
Validation	
Correct equipment available	
Equipment/supplies/manuals available to lubricate, calibrate, maintain, and repair	

Chapter VI

EQUIPMENT

Concept and objective

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

Equipment should be installed in such a way as to minimize any risk of error or of contamination. Fixed pipe-work should be clearly labeled to indicate the contents and, where applicable, the direction of flow. All service piping and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.

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

Production equipment should be designed, located, and maintained to serve its intended purpose. They should be designed so that they can be easily and thoroughly cleaned on a scheduled basis.

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

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

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

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

Materials used for cooling or for lubrication (grease) should not be cross mixed with the starting materials, pharmaceutical products, packaging materials or packaged products.

Liquid filtration should not release any filter media fiber to the liquid or solution to be filtered. The asbestos filter should not absolutely be used for liquid filtration or for any purpose in the factory. It is preferable also to use the automatic multipurpose device, with routine testing of its efficiency and validity according to a fixed recorded program.

There should be a device to avoid any problem reflected by inflammable materials.

Location and separation of equipment

The equipment should be separated from each other by certain partition to prevent mixing and/or cross contamination. Water, steam, pressure and vacuum pipes should be covered, isolated and colored to be easily recognized. Steam pipes should be supplied with steam traps and drainage for water. Conveyor and belt conveyor should be provided with special security measures.

Cleaning and maintenance

Equipment and containers should be kept clean and maintained according to a fixed written schedule to prevent its inefficiency. The cleaning and maintenance methods should offer the following

- Cleaning and maintenance responsibilities.
- Cleaning maintenance programs should be easy and clear.
- Dis-and reassembling of equipment should be described in details (if necessary).
- Method for the removal of the relevant materials from the previous batches before the next batch.
- How to keep the equipment cleaned dining and after operations.
- Inspection of the equipment just before and after operations.

Automatic and electronic equipment

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. In case of using computer for recording the batch record, all the batch changes should be registered with the assurance of continuous validity of what have been recorded on the device.

Validity of the device

Validity system should be applied to all the equipment that are characterized by variation in its performance specially balances, different filtration devices, sterilization, mixing, homogenization, quality control equipment and others, complying to fixed program each according to its variation probabilities with special record for each device to be established.

Utilities and services

1. Water

Four types of water supply are normally used in a pharmaceutical plant

a. Potable (Mains) Water.

b. Purified Water (De-mineralized or Distilled)

c. Water for Injection.

d. Cooling Water.

All types of water should be monitored for chemical and microbiological purity at frequent intervals. Formal procedures should be established for the sampling and testing of water. Written warning and action limits should be agreed between quality control, production and engineering management, including procedures to be taken when the quality falls below these limits.

Records should be maintained of the results of all testing, and made available to relevant personnel. All “points of use” should

be opened and allowed to flow for a minimum of one minute at least once per day.

a. Potable water

It is the normal source of water for drinking, and hand-washing purposes. It should be supplied under continuous positive pressure. Particular care is necessary whenever a storage tank is provided in the system (e.g. in the case of a hot water supply tank). This can act as a focus for microbial growth, and particular vigilance should be maintained with routine quality monitoring.

b. Purified water

Purified Water is normally produced by exchange treatment, distillation and/or reverse osmosis. The use of ion-exchange or reverse osmosis may increase the risk of microbial contamination unless suitable precautions are taken. Ion-exchange columns are particularly vulnerable to bacterial contamination, and acid/base regeneration should be frequent to reduce the risks. Frequent chemical and microbial monitoring of such systems is essential.

Wherever possible the water in the distribution system would be kept in circulation to avoid the build-up foci of bacterial growth and maintained above 80 °C. In these cases, localized cooling at the off-take points is usually necessary. Particular care must be taken to ensure that cooling water does not contaminate the purified water. Where storage tanks are used rapid turn around of contents must occur.

The use of in-line ultra-violet radiation within the circulating system to reduce the proliferation of microorganisms may also be considered but its efficacy has been queried, particularly if the water does not flow in the normal manner in a well designed system.

Stainless steel piping (normally passivated 316 grade) is the material of choice for the distribution system although it is very expensive for large systems. A disadvantage of stainless steel is lack of resistance to hypochlorite. Its advantages, however, for both purified water and water for injections systems are

- Minimum joints - since the system can be smooth-welded.
- Steam sterilizable.
- Chemically resistant to many sanitizing agents.
- Tough and resistant to mechanical damage.

If plastic pipe-work is utilized it should be solvent welded and be capable of effective sanitation. Particular care should be given to the design of the distribution system to ensure that

- The system can be sterilized (by steam or other means).
- Dead legs are minimized (maximum dead leg length of 6 pipe diameters is recommended).
- Lines are sloped to permit free drainage.
- Low points of the system are drainable.
- Flow rate in relation to pipe diameter should be designed to avoid microbial build up.

c. Water for injections

Water for injections is normally produced by distillation of potable water or purified water, usually by means of multiple-effect still. This ensures that entrainment of water droplets is avoided, and that water is produced free from pyrogens. The water should be kept circulated at a temperature over 80 °C under ultraviolet. It should be used within 24 hours.

Systems should be monitored frequently for absence of pyrogens, usually on a daily basis when the water is being used in production processes. Testing in rabbits or using the Limulus Amoebocyte Lysate (LAL) test may be utilized; the latter is usually to be preferred because of more rapid result generation, reduced costs and enhanced sensitivity.

Water for injections should have facilities to monitor storage temperature. Storage tanks for the storage of purified water or water for injections require venting to prevent their collapse when water is withdrawn. This is normally accomplished using a 0.45 micron or 0.22 micron hydrophobic bacterial retentive filter.

Water for injections should be kept in sterile container, which does not interact, nor interfere but protect water from any contamination. Keeping inside system is preferable.

d. Cooling water

Water used in the chamber of autoclaves as a coolant after the sterilization cycle should conform to the standards of water for injections, specified in the pharmacopoeias and be treated to

eliminate microorganisms and should not alter the safety of drug product.

2. Steam

Steam is used for a variety of purposes within a pharmaceutical plant including

- Environmental heating.
- Process temperature control, e.g. steam-jacketed vessels, heating coils, etc.
- Cleaning, e.g. steam cleaning, or as admixture with water.
- Sterilization, e.g. "live-steaming" of vessels pipelines, autovalving, ethylene oxide sterilization.

Pipelines and valves carrying steam should be tagged and clearly identified. The differentiation between high-pressure and low-pressure steam should be obvious by clear labeling. Attention must be given to valve joint maintenance and valve design.

Steam mains should have expansion joints or loop's bends and must be laid to a defined gradient. Condensation traps should be present on all equipment and at suitable points in the supply lines.

The quality of steam which comes into contact with the product or pack should be monitored regularly and at frequent intervals. Where necessary, the steam should be filtered.

When used as a sterilant in autoclaves, the condensed steam should comply with the monograph for water for injections, specified in the pharmacopoeias and be free from condensable

gases. Care should be taken to avoid superheating when using steam for surface sterilization.

3. Electricity

Electricity is one of the most universal utility needs in a modern pharmaceutical plant. Critical areas should have adequate back-up systems in the event of a mains failure. The changeover time should be minimal. A list of critical areas and items should be agreed between production, engineering and quality assurance management.

Action to be taken in emergency situations should be agreed and published, and names and telephone numbers of key personnel should be made available to relevant staff (security staff, production and engineering supervisors, etc.)

Certain equipment (microprocessors, analytical instruments, etc.) may require voltage stabilization to ensure reproducibility of operation.

Chapter VII

PRODUCTION

Concept and objective

Production operations must follow clearly defined procedures. Standard operation procedures should be written for all production stages. The following should be agreed, specified and documented in accordance with relevant company and/or legislative requirements before processing is initiated.

- Specifications and sources for the starting materials.
- The system for ordering, handling, storing and approving starting materials prior to use.
- Standards for facilities and process equipment (normally in terms of construction, installation, operation and performance).
- The master formula and method of manufacture written in a clear and unambiguous manner.
- Commissioning and qualification results obtained for the facilities and manufacturing equipment.
- Process validation data for the plant to be used for the full-scale process.
- Acceptable ranges for key facility and process variables which have been established during the course of commissioning, qualification and validation.
- In-process control and monitoring systems.
- Cleaning procedures for process plant and facilities.

- Product inspection systems and associated standards.
- Supplementary standard operating procedures for all important activities not covered by the method of manufacture.
- Specifications for the partially finished product (where appropriate).
- "Release and check" specifications for the finished product.
- Storage systems and conditions to protect the integrity and quality of products at all processing stages.
- Systems for ensuring that adequate batch records are completed, checked, and stored.
- Systems for ensuring that the personnel controlling and carrying out the process are suitably qualified and properly trained.
- Systems and procedures to ensure safe working practices.
- Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.
- At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate the rooms used should be labeled or otherwise identified with an indication of the product or material being processed, its strength (where applicable), and the batch number. Where applicable, this indication should also mention the stage of production.

- Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.
- Where systems have a direct influence on product quality, they should be approved by persons responsible for production and quality control. Other items may need the approval of those responsible for research, development, engineering and safety, as appropriate.
- Documents such as master formulae and methods, specifications, validation protocols and reports and master batch records should be formally approved before use by the persons responsible for production and quality control.

Validity of the production method

The validity of the production method, introduced by the research and development department should be assured in case of

- Using new production procedures, new raw material or new equipment
- Essential change in the main lines.

There should be periodical evaluation to assure the validity of the method.

Batch number system

- There should be a special number for each batch.
- The number given to a batch should not be repeated.

- Batch numbers and volume should be recorded in special records.

Measuring out (dispensing)

The measuring out of raw materials for use in pharmaceutical processes is a fundamentally important activity which, if correctly performed should provide a high degree assurance as to the composition of finished products.

Measuring out of raw materials must be done

- According to formally defined procedures.
- Using relevant batch documents and records.
- By trained and authorized personnel.
- In an environment that avoids contamination and preserves the integrity of the materials being handled.
- Using calibrated and properly maintained equipment.
- Under the general standard of environmental control and hygiene appropriate to the finished product in which they are to be used.

Centralization of measuring out activities within the manufacturing unit may be an efficient and convenient means of handling materials. Care must be taken to ensure that the measuring system used is of sufficient capacity, accuracy and sensitivity for the amounts being measured. This applies to scales, load cells, flow-meters, volumetric measures, and level sensors/indicators.

The calibration of weighing and measuring systems must be carried out at regular intervals in accordance with a written schedule, and must be recorded. In addition to checks on the actual weighing or measuring operation, further checks should be carried out and recorded for

- The labeling of the containers from which measuring out is performed (name, batch number, grade, code number and, where applicable, quality status).
- The labeling of the materials when measured out (name, batch number, grade, code number and batch in which it is to be used).
- The quantities measured out compared with those required.
- The net amount of the measured out material and the tare and gross of the container.
- The reconciliation of the amounts used and those remaining against the initial stock holding.

All of the checks should involve two operators, one performing the operation, the second double-checking, with both recording the results in the batch records. However, for certain operations, electronic checking and recording systems provide an opportunity for omitting the second check.

Checks on labeling, condition and quantity should be carried out when containers of measured out materials are received by the manufacturing unit. To prevent mixing between materials in preparation area the following precautions must be taken

- Not more than one material to be handled at the same time.

- When any package is transferred from the raw material store to the preparation area, this requires confirmation from the label.
- Weighing should be done by two persons separately.
- Preparation area and its balances should be kept clean.
- Weighing must be carried out by clean balances and equipment.
- After weighing, the packages returned back to the store must be confirmed from the labels which bear contents. In case of materials left for long time reconfirmation for its content must be carried out by the quality control department.

Cross-contamination and bacterial contamination in production

Cross contamination is the unwanted presence of a material, component or product in another raw material, component or product. It may arise from activities associated with the item under consideration or from extraneous sources. When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Cross contamination may be caused by the release of dust, gases, vapors, sprays or organisms from materials and processes, from residues in equipment, from operators' clothing, from operators, from the environment, from utilities and from other external sources.

Cross contamination should be absent from medicinal products but in practice it cannot be eliminated. Moreover monitoring, and hence control, is only possible within the limits of detection for known and potential contaminants. The significance of

cross contamination should be assessed in relation to the chemical, physiological and microbiological effects of the known contaminant in relation to the characteristics and use of the product in which it is present.

In preventing cross contamination, particular emphasis should be placed on good practices in the handling of highly potent and toxic materials or sensitizing agents used in manufacture (such as hormones, cytotoxic products, certain antibiotics and biological materials). 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 penicillin, 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.

Measures to prevent cross-contamination and their effectiveness should be checked periodically according to standard operating procedures. Production areas where susceptible products are processed should undergo periodic microbiological monitoring.

Manufacturing

A. Intermediate and bulk products

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. Any necessary in-process controls and environmental controls should be carried out and recorded. Constituents "raw materials or labels" of each batch must be put in a closed cage or cages to be transferred to the concerning production site, accompanied with all data related to the batch.

All packaging materials must be checked before use in each production batch. Raw materials must be checked twice from packaging and weighing point of view and be sure that both packaging data and weight comply with the documented data of the concerned batch. The conditions of production unit must comply with all the specified conditions (e.g. temperature, relative humidity, air flow ability, class-requirements, etc).

All machines and devices used for production and support sections must comply with the specified validated standards. The

written procedure should be followed in all steps of production, analysis, controlling and in case of any changes, these changes must be approved and recorded in a written way by reasons from the concerned persons or committee. It should be confirmed that all preparation containers are clean, carry code numbers or cards and confirm the clearance of the previous numbers or cards.

After termination of the preparation, packages are put in the quarantine area till allowed to transfer to the final product warehouse. The actual volume of production should be mentioned and compared with the calculated volume and in case of fundamental difference between the actual and the theoretical volumes, reasons must be mentioned and parameters should be issued to prevent such big difference in future. Under all conditions all precautions should be taken to prevent cross mixing of any batch.

Re-manufacturing

In case of re-manufacturing for the products which are not passed by quality control, the new method for re-manufacturing process should be recorded at any production step. Re-manufacturing should not be carried out without approval of concerning authority of quality control department.

Time of manufacturing

The timing of some manufacturing steps must be fixed, especially those which are strongly affected by the time factor such as mixing operations. In case of varying any specified procedure, time must be recorded in operation sheet with reasons.

B. Solid products

Circulating air of solid product and powder preparation area must be isolated to prevent cross mixing of air. All air handling units and filters used must be periodically validated. Powders must not be contaminated by metal particles and the glassy tools must not be used with the continued inspection of sieves and any utensils in direct contact with powders to be sure that they are not injured before and after manufacturing process.

Tablets and capsules which are invisible inside the manufacturing machine must not be ejected without notice. Dust-vacuum devices must be available. Relative humidity and temperature must be fixed at the specified level for each batch.

Mixing, granulation, drying

If the processes of mixing and sieving are not isolated, dust-vacuum devices must be available. Mixing time, temperature and relative humidity must be fixed as mentioned in the preparation steps. Filters for driers, if any, must be controlled and assured for their clean condition. Sensitive materials need specified filters. All precautions must be taken to prevent microbial contamination for the solutions used in granulation process. Specified humidity percentage must be kept in the dried granules. The granules should not be exposed to any external factors that may change humidity. Under all conditions all precautions must be taken to prevent cross mixing between different batches.

Compression

Compression machines must be isolated with the dust vacuum device which must be available. If compression machine is not isolated, circulating air of its area must be separated. Control test devices must be available during manufacturing processes. Any rejected tablet samples must not be returned and its number should be mentioned in the batch documents. Compression machine should be checked before use. All precautions must be taken to prevent cross-mixing.

Coating

The air used for drying of tablets should be filtered. Vapor limits initiated from solvents of coating materials must not exceed the healthy specified limits.

The conditions must be adjusted to prevent microbial contamination of coating solutions, to prevent evaporation of solvents and to prevent any reaction with the container.

Hard and soft gelatin capsules

Capsule machine should be isolated. In case of soft gelatin capsules care should be taken regarding the oil supply and the waste products. Extreme of humidity and temperature should be avoided. High humidity (> 60% RH at 21-24 °C) produces more lasting effects on the capsule shell, since as moisture is absorbed, the capsules become softer, tackier and bloated. Capsules should be stored in an-air conditioned area in which the humidity does not exceed 45% RH at 21- 24 °C.

Empty hard gelatin capsules, generally range in moisture content between 12-15%. Exposure to either heat or moisture extremes can distort empty capsules to the extent that they can not be handled by automatic filling machine. All precautions must be taken to prevent cross mixing during packing. Inspection during polishing of capsules and coated tablets is essential.

C. Solutions, creams, ointments and other local preparations

Liquids, creams and ointments should be manufactured so as to protect the product from microbial and other contamination. The use of closed systems of manufacture and transfer is recommended where possible. Water used for the manufacturing should comply with the specifications of the pharmacopoeias for salts and microorganisms limitations. All pipes used for the transfer of solid sugar, water or other solutions must be easily cleaned and maintained and should have the facilities to assure the arrival of the material to the desired place.

Where pipe lines are used to transfer bulk materials to remote holding vessels or filling machines it must be ensured that the material is, in fact, delivered to the intended vessel or machine. Care should be taken, when bulk tanker deliveries are received, to ensure the quality and quantity of the delivery before use. The instruments that can be cleaned in its place are always preferable. All measurement instruments should be calibrated and validated, also it is possible to use a dipping measure in case the container permits that, but it must not react or adsorb the active constituents.

Manufacture of sterile medicinal products

Principle

The manufacture of sterile products is subject to special requirements in order to minimize risks of microbiological contamination, and of particulate and pyrogen contamination. Much depends on the skill, training and attitudes of the personnel involved. Quality Assurance bears a particularly great importance and this type of manufacture must strictly follow carefully established and validated methods of preparation and procedure. Sole reliance for sterility or other quality aspects must not be placed on any terminal process or finished product test. This section does not lay down detailed methods for determining the microbiological and particulate cleanliness of air, surfaces, etc. Reference is made to other compendia such as the CEN/ISO standards.

General

1. The manufacture of sterile products should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate cleanliness standard and supplied with air which has passed through filters of an appropriate efficiency.

2. The various operations of component preparation, product preparation and filling should be carried out in separate areas within the clean area. Manufacturing operations are divided into two categories; firstly those where the product is terminally sterilized, and secondly those which are conducted aseptically at some or all stages.

3. Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing operation requires an appropriate environmental cleanliness level in the operational state in order to minimize the risks of particulate or microbial contamination of the product or materials being handled.

In order to meet "in operation" conditions these areas should be designed to reach certain specified air-cleanliness levels in the "at rest" occupancy state. The "at-rest' state is the condition where the installation is complete with production equipment installed and operating but with no operating personnel present. The "in operation" state is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.

For the manufacture of sterile medicinal products normally 4 grades can be distinguished.

Grade A The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide a homogeneous air speed of 0.45 m/s ± 20% (guidance value) at the working position.

Grade B In case of aseptic preparation and filling the background environment of Grade A zone.

Grade C and D Clean areas for carrying out less critical stages in the manufacture of sterile products.

The airborne particulate classification for these grades is given in the following table.

	At rest [b]		In operation	
Grade	**Maximum permitted number of particles/m^3 equal to or above**			
	0.5 µm	5 µm	0.5 µm	5 µ
A	3 500	0	3 500	0
B [a]	3 500	0	350 000	2 000
C [a]	350 000	2 000	3 500 000	20 000
D [a]	3 500 000	20 000	not defined [c]	not defined [c]

[a] In order to reach the B, C and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate filters such as HEPA for grades A, B and C.

[b] The guidance given for the maximum permitted number of particles in the "at rest" condition corresponds approximately to the US Federal Standard 209 E and the ISO classifications as follows grades A and B correspond with class 100, M 3.5, ISO 5; grade C with class 10000, M 5.5, ISO 7 and grade D with class 100000, M 6.5, ISO 8.

[c] The requirement and limit for this area will depend on the nature of the operations carried out.

Examples of operations to be carried out in the various grades are given in the table below

Grade	Examples of operations for terminally sterilized products
A	Filling of products, when unusually at risk
C	Preparation of solutions, when unusually at risk. Filling of products
D	Preparation of solutions and components for subsequent filling

Grade	Examples of operations for aseptic preparations
A	Aseptic preparation and filling
C	Preparation of solutions to be filtered
D	Handling of components after washing

The particulate conditions given in the table for the "at-rest" state should be achieved in the unmanned state after a short "clean up" period of 15-20 minutes (guidance value), after completion of operations. The particulate conditions for grade A in operation given in the table should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, due to the generation of particles or droplets from the product itself.

4. In order to control the particulate cleanliness of the various grades in operation, the areas should be monitored.

5. In order to control the microbiological cleanliness of the various grades in operation, the areas should be monitored.

Where aseptic operations are performed monitoring should be frequent using methods such as settle plates, volumetric air and surface sampling (e.g. swabs and contact plates). Sampling methods used in operation should not interfere with zone protection. Results from monitoring should be considered when reviewing batch documentation for finished product release. Surfaces and personnel should be monitored after critical operations.

Additional microbiological monitoring is also required outside operations, e.g. after validation of systems, cleaning and sanitation.

Recommended limits for microbiological monitoring of clean areas in operation

Recommended limits for microbial contamination [a]				
Grade	**Air sample cfu/m^3**	**Settle plates (diam. 90 mm) cfu/4 hours [b]**	**Contact plates (diam. 55 mm) cfu/plate**	**Glove print 5 fingers cfu/glove**
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

[a] These are average values

[b] Individual settle plates may be exposed for less than 4 hours

6. Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded operating procedures should prescribe corrective action.

Isolator technology

7. The utilization of isolator technology to minimize human interventions in processing areas may result in a significant decrease in the risk of microbiological contamination of aseptically manufactured products from the environment. There are many possible designs of isolators and transfer devices. The isolator and the background environment should be designed so that the required air quality for the respective zones can be realized. Isolators are constructed of various materials more or less prone to puncture and leakage. Transfer devices may vary from a single door to double door designs to fully sealed systems incorporating sterilization mechanisms.

The transfer of materials into and out of the unit is one of the greatest sources of contamination. In general the area inside the isolator is the local zone for high risk manipulations although it is recognized that laminar air flow may not exist in the working zone of all such devices. The air classification required for the background environment depends on the design of the isolator and its application. It should be controlled and for aseptic processing be at least grade D.

8. Isolators should be introduced only after appropriate validation. Validation should take into account all critical factors of isolator technology, for example the quality of the air inside and outside (background) the isolator, sanitation of the isolator, the transfer process and isolator integrity.

9. Monitoring should be carried out routinely and include frequent leak testing of the isolator and glove/sleeve system.

Blow, fill, and seal technology

10. Blow/fill/seal units are purpose built machines in which, in one continuous operation, containers are formed from a thermoplastic granulate, filled and then sealed, all by the one automatic machine. Blow/fill/seal equipment used for aseptic production which is fitted with an effective grade A air shower may be installed in at least a grade C environment, provided that grade A/B clothing is used. The environment should comply with the viable and non-viable limits at-rest and the viable limit only when in operation. Blow/fill/seal equipment used for the production of products for terminal sterilization should be installed in at least a grade D environment.

Because of this special technology particular attention should be paid to at least the following equipment design and qualification, validation and reproducibility of cleaning-in-place and sterilization-in-place, background clean room environment in which the equipment is located, operator training and clothing, and interventions in the critical zone of the equipment including any aseptic assembly prior to the commencement of filling.

Terminally sterilized products

11. Preparation of components and most products should be done in at least a grade D environment in order to give low risk of microbial and particulate contamination, suitable for filtration and sterilization. Where there is unusual risk to the product because of microbial contamination, for example, because the product actively supports microbial growth or must be held for a long period before sterilization or is necessarily processed not mainly in closed vessels, preparation should be done in a grade C environment. Filling of products for

terminal sterilization should be done in at least a grade C environment. Where the product is at unusual risk of contamination from the environment, for example because the filling operation is slow or the containers are wide-necked or are necessarily exposed for more than a few seconds before sealing, the filling should be done in a grade A zone with at least a grade C background. Preparation and filling of ointments, creams, suspensions and emulsions should generally be done in a grade C environment before terminal sterilization.

Aseptic preparation

12. Components after washing should be handled in at least a grade D environment. Handling of sterile starting materials and components, unless subjected to sterilization or filtration through a micro-organism-retaining filter later in the process, should be done in a grade A environment with grade B background. Preparation of solutions which are to be sterile filtered during the process should be done in a grade C environment; if not filtered, the preparation of materials and products should be done in a grade A environment with a grade B background. Handling and filling of aseptically prepared products should be done in a grade A environment with a grade B background. Transfer of partially closed containers, as used in freeze drying, should, prior to the completion of stoppering, be done either in a grade A environment with grade B background or in sealed transfer trays in a grade B environment. Preparation and filling of sterile ointments, creams, suspensions and emulsions should be done in a grade A environment, with a grade B

background, when the product is exposed and is not subsequently filtered.

Personnel

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

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

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

16. High-standards of personnel hygiene and cleanliness are essential. Personnel involved in the manufacture of sterile preparations should be instructed to report any condition which may cause the shedding of abnormal numbers or types of contaminants; periodic health checks for such conditions are desirable. Actions to be taken about personnel who could be introducing undue

microbiological hazard should be decided by a designated competent person.

17. Changing and washing should follow a written procedure designed to minimize contamination of clean area clothing or carry-through of contaminants to the clean areas.

18. Wristwatches, make-up and jeweler should not be worn in clean areas.

19. The clothing and its quality should be appropriate for the process and the grade of the working area. It should be worn in such a way as to protect the product from contamination. The description of clothing required for each grade is given below

Grade D Hair and, where relevant, beard should be covered. A general protective suit and appropriate shoes or overshoes should be worn. Appropriate measures should be taken to avoid any contamination coming from outside the clean area.

Grade C Hair and, where relevant, beard and moustache should be covered. A single or two-piece trouser suit, gathered at the wrists and with high neck and appropriate shoes or overshoes should be worn. They should shed virtually no fibers or particulate matter.

Grade A/B Headgear should totally enclose hair and, where relevant, beard and moustache; it should be tucked into the neck of the suit; a face mask should be worn to prevent the shedding of droplets. Appropriate sterilized, non-powdered rubber or plastic gloves and sterilized or disinfected footwear should be worn. Trouser-buttons should be tucked inside the footwear and garment

sleeves into the gloves. The protective clothing should shed virtually no fibers or particulate matter and retain particles shed by the body.

20. Outdoor clothing should not be brought into changing rooms leading to grade B and C rooms. For every worker in a grade A/B area, clean sterile (sterilized or adequately sanitized) protective garments should be provided 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 changed at least at every working session.

21. Clean area clothing should be cleaned and handled in such a way that it does not gather additional contaminants which can later be shed. These operations should follow written procedures. Separate laundry facilities for such clothing are desirable. Inappropriate treatment of clothing will damage fibers and may increase the risk of shedding of particles.

Premises

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

23. To reduce accumulation of dust and to facilitate cleaning there should be no un-cleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment. Doors should be designed to avoid those un-cleanable recesses; sliding doors may be undesirable for this reason.

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

25. Pipes and ducts and other utilities should be installed so that they do not create recesses, unsealed openings and surfaces which are difficult to clean.

26. Sinks and drains should be prohibited in grade A/B areas used for aseptic manufacture. In other areas air breaks should be fitted between the machine or sink and the drains. Floor drains in lower grade clean rooms should be fitted with traps or water seals to prevent back-flow.

27. Changing rooms should be designed as airlocks and used to provide physical separation of the different stages of changing and so minimize microbial and particulate contamination of protective clothing. They should be flushed effectively with filtered air. The final stage of the changing room should, in the at-rest state, be the same grade as the area in into which it leads. The use of separate changing rooms or entering and leaving clean areas is sometimes desirable. In general hand washing facilities should be provided only in the first stage of the changing rooms.

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

29. A filtered air supply should maintain a positive pressure and an air flow relative to surrounding areas of a lower grade under all operational conditions and should flush the area effectively. Adjacent rooms of different grades should have a pressure differential of 10-

15 Pascal's (guidance values). Particular attention should be paid to the protection of the zone of greatest risk, that is, the immediate environment to which a product and cleaned components which contact the product are exposed. The various recommendations regarding air supplies and pressure differentials may need to be modified where it becomes necessary to contain some materials, e.g. pathogenic, highly toxic, radioactive or live viral or bacterial materials or products. Decontamination of facilities and treatment of air leaving a clean area may be necessary for some operations.

30. It should be demonstrated that air-flow patterns do not present a contamination risk, e.g. care should be taken to ensure that air flows do not distribute particles from a particle-generating person, operation or machine to a zone of higher product risk.

31. A warning system should be provided to indicate failure in the air supply. Indicators of pressure differences should be fitted between areas where these differences are important. These pressure differences should be recorded regularly or otherwise documented.

Equipment

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

33. As far as practicable, equipment, fittings and services should be designed and installed so that operations, maintenance and repairs can be carried out outside the clean area. If sterilization is required, it should be carried out after complete reassembly wherever possible.

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

35. Water treatment plants and distribution systems should be designed, constructed and maintained so as to ensure a reliable source of water of an appropriate quality. They should not be operated beyond their designed capacity. Water for injection should be produced, stored, and distributed in a manner which prevents microbial growth, for example by constant circulation at a temperature above 70 °C.

36. All equipment such as sterilizers, air handling and filtration systems, air vent and gas filters, water treatment, generation, storage and distribution systems should be subject to validation and planned maintenance; their returning to use should be approved.

Sanitation

37. The sanitation of clean areas is particularly important. They should be cleaned thoroughly in accordance with a written program. Where disinfectants are used, more than one type should be employed. Monitoring should be undertaken regularly in order to detect the development resistant strains.

38. Disinfectants and detergents should be monitored for microbial contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless

sterilized. Disinfectants and detergents used in Grades A and B areas should be sterile prior to use.

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

Processing

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

41. Preparations of microbiological origin should not be made or filled in areas used for the processing of other medicinal products; however, vaccines of dead organisms or of bacterial extracts may be filled, after inactivation, in the same premises as other sterile medicinal products.

42. Validation of aseptic processing should include a process simulation test using a nutrient medium (media fill). Selection of the nutrient medium should be made based on dosage form of the product and selectivity, clarity, concentration and suitability for sterilization of the nutrient medium. The process simulation test should imitate as closely as possible the routine aseptic manufacturing process and include all the critical subsequent manufacturing steps. It should also take into account various interventions known to occur during normal production as well as worst case situations. Process simulation tests should be performed as initial validation with three consecutive satisfactory simulation tests per shift and repeated at defined intervals and after any significant modification to the HVAC-system, equipment, process and number of shifts. Normally process simulation tests should be

repeated twice a year per shift and process. The number of containers used for media fills should be sufficient to enable a valid evaluation. For small batches, the number of containers for media fills should at least equal the size of the product batch. The target should be zero growth but a contamination rate of less than 0.1% with 95% confidence limit is acceptable. The manufacturer should establish alert and action limits. Any contamination should be investigated.

43. Care should be taken that any validation does not compromise the processes.

44. Water sources, water treatment equipment and treated water should be monitored regularly for chemical and biological contamination and, as appropriate, for endotoxins. Records should be maintained of the results of the monitoring and of any action taken.

45. Activities in clean areas and especially when aseptic operations are in progress should be kept to a minimum and movement of personnel should be controlled and methodical, to avoid excessive shedding of particles and organisms due to over-vigorous activity. The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.

46. Microbiological contamination of starting materials should be minimal. Specifications should include requirements for microbiological quality when the need for this has been indicated by monitoring.

47. Containers and materials liable to generate fibers should be minimized in clean areas.

48. Where appropriate, measures should be taken to minimize the particulate contamination of the end product.

49. Components, containers and equipment should be handled after the final cleaning process in such a way that they are not re-contaminated.

50. The interval between the washing and drying and the sterilization of components, containers and equipment as well as between their sterilization and use should be minimized and subject to a time-limit appropriate to the storage conditions.

51. The time between the start of the preparation of a solution and its sterilization or filtration through a micro-organism-retaining filter should be minimized. There should be a set maximum permissible time for each product that takes into account its composition and the prescribed method of storage.

52. The bio-burden should be monitored before sterilization. There should be working limits on contamination immediately before sterilization which are related to the efficiency of the method to be used. Where appropriate the absence of pyrogens should be monitored. All solutions, in particular large volume infusion fluids, should be passed through a micro-organism-retaining filter, if possible sited immediately before filling.

53. Components, containers, equipment and any other article required in a clean area where aseptic work takes place should be sterilized and passed into the area through double-ended sterilizers

sealed into the wall, or by a procedure which achieves the same objective of not introducing contamination. Non-combustible gases should be passed through micro-organism retentive filters.

54. The efficacy of any new procedure should be validated, and the validation verified at scheduled intervals based on performance history or when any significant change is made in the process or equipment.

Sterilization

55. All sterilization processes should be validated. Particular attention should be given when the adopted sterilization method is not described in the current edition of the European Pharmacopoeia, or when it is used for a product which is not a simple aqueous or oily solution. Where possible, heat sterilization is the method of choice. In any case, the sterilization process must be in accordance with the marketing and manufacturing authorizations.

56. Before any sterilization process is adopted its suitability for the product and its efficacy in achieving the desired sterilizing conditions in all parts of each type of load to be processed should be demonstrated by physical measurements and by biological indicators where appropriate. The validity of the process should be verified at scheduled intervals, at least annually, and whenever significant modifications have been made to the equipment. Records should be kept of the results.

57. For effective sterilization the whole of the material must be subjected to the required treatment and the process should be designed to ensure that this is achieved.

58. Validated loading patterns should be established for all sterilization processes.

59. Biological indicators should be considered as an additional method for monitoring the sterilization. They should be stored and used according to the manufacturers' instructions, and their quality checked by positive controls. If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination from them.

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

61. Sterilization records should be available for each sterilization run. They should be approved as part of the batch release procedure.

Sterilization by heat

62. Each heat sterilization cycle should be recorded on a time/temperature chart with a suitably large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling and/or recording should have been determined during the validation and, where applicable, also checked against a second independent temperature probe located at the same position.

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

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

65. 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.

Moist heat

66. Both temperature end pressure should be used to monitor the process. Control instrumentation should normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications they should be validated to ensure that critical process requirements are met. System and cycle faults should be registered by the system and observed by the operator. The reading of the independent temperature indicator should be 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 frequent leak tests on the chamber when a vacuum phase is part of the cycle.

67. The items to be sterilized, other than products in sealed containers, should be wrapped in a material which allows removal of air and penetration of steam but which prevents recontamination after sterilization. All parts of the load should be in contact with the sterilizing agent at the required temperature for the required time.

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

Dry heat

69. The process used should include air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted should be passed through a HEPA filter. Where this process is also intended to remove pyrogens, challenge tests using endotoxins should be used as part of the validation.

Sterilization by radiation

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

71. During the sterilization procedure the radiation dose should be measured. For this purpose, dosimetry indicators which are independent of dose rate should be used, giving a quantitative

measurement of the dose received by the product itself. Dosimeters should be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the irradiator. Where plastic dosimeters are used they should be used within the time-limit of their calibration. Dosimeter absorbance should be read within a short period after exposure to radiation.

72. Biological indicators may be used as an additional control.

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

74. Materials handling procedures should prevent mix-up between irradiated and non-irradiated materials. Radiation-sensitive color disks should also be used on each package to differentiate between packages which have been subjected to irradiation and those which have not.

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

Sterilization with ethylene oxide

76. This method should only be used when no other method is practicable. During process validation it should be shown that there is 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.

77. 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.

78. 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.

79. 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.

80. 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 and of the total amount of gas used. The pressure and temperature should be recorded throughout the cycle on a chart. The record(s) should form part of the batch record.

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

Filtration of medicinal products which cannot be sterilized in their final container

82. Filtration alone is not considered sufficient when sterilization in the final container is possible. With regard to methods currently available, steam sterilization is to be preferred. If the product cannot

be sterilized in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilized container. Such filters can remove most bacteria and moulds, but not all viruses or mycoplasma. Consideration should be given to complementing the filtration process with some degree of heat treatment.

83. Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration via a further sterilized micro-organism 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.

84. Fiber shedding characteristics of filters should be minimal.

85. The integrity of the sterilized filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences during routine manufacturing from this should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.

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

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

Finishing of sterile products

88. Containers should be closed by appropriately validated methods. Containers closed by fusion, e.g. glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures.

89. Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period.

90. Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects. 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 eye-sight 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. Results should be recorded.

Quality control

91. The sterility test applied to the finished product should only be regarded as the last in a series of control measures by which sterility is assured. The test should be validated for the product(s) concerned.

92. In those cases where parametric release has been authorized, special attention should be paid to the validation and the monitoring of the entire manufacturing process.

93. Samples taken for sterility testing should be representative of the whole of the batch, but should in particular include samples taken from parts of the batch considered to be most at risk of contamination, e.g.

a) for products which have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant intervention;

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

Checklist for premises of mixing and formulation

Facilities	**Status**
General cleanliness of area	
No leaks, holes, cracks in building/windows	
No insects/rodents	
No unrelated traffic/pedestrian flow	
Area secured behind closed doors	
Floors/walls covered with material to facilitate cleaning	
Size of facility adequate	
Separate area for Storage of approved raw materials	
Weighing/re-checking/QC.	
Storage of mixed/bulk formulated batches awaiting transfer	
Special storage for special requirements	
QA/QC testing of intermediates	
Necessary utilities in sufficient quality and quantity	
Adequate lighting and ventilation	

Checklist for personnel working in mixing and formulation

Personnel	**Status**
Determine minimum number of personnel needed	
Position Description (PD) for each employee	
Chart key functions/personnel	
Identify basic qualification for each PD	
Identify special skills for each PD	
Identify key staff and delegate/assign responsibilities needed for proper functioning e.g. supervising/training/ maintenance	
Develop training program	
Schedule periodic retraining	
Schedule periodic performance evaluations	

Checklist for equipment of mixing and formulation

Equipment	Status
Dedicated equipment available for Lifting and transporting	
Special storage-constant room temperature	
Measuring/weighing/sampling	
Laboratory testing	
Cleaning equipment	
Sterilizers/autoclaves	
Mixing machinery	
Drying equipment	
Granulation/re-granulation	
Sealable containers for storage/transfer to mixed batches to final dosage form preparation area	
Equipment in good working order	
Cleanliness	
Maintenance according to schedule	
Calibration	
Validation	
Correct equipment available	
Equipment/ supplies/ manuals available to lubricate, calibrate, maintain, and repair	

Checklist for personnel working in finished dosage form preparations

Personnel	**Status**
Determine minimum number of personnel needed	
Position Description (PD) for each employee	
Chart key functions/personnel	
Identify basic qualification for each PD	
Identify special skills for each PD	
Identify key staff and delegate/ assign responsibilities needed for proper functioning e.g. supervising/training/ maintenance.	
Develop training program	
Schedule periodic retraining	
Schedule periodic performance evaluations	

Checklist for equipment of finished dosage form preparations

Equipment	Status
Dedicated equipment available for Lifting and transporting	
Special storage-constant room temperature	
Measuring/weighing/sampling	
Laboratory testing	
Cleaning equipment	
Tableting, encapsulating and powder packaging machinery	
Sterilization	
Sealable containers for storage transfer to mixed batches to final dosage form preparation area	
Granulation/re-granulation	
Sealable containers for storage/transfer to mixed batches to final dosage form preparation area	
Equipment in good working order	
Cleanliness	
Maintenance/lubrication according to schedule	
Calibration	
Validation	
Critical equipment (punches, dies, etc.) special handling procedures	
Correct equipment available	
Equipment/ supplies/ manuals available to lubricate, calibrate, maintain, and repair	

Checklist for premises of finished goods, storage and warehousing

Facilities	**Status**
General cleanliness of area	
No leaks, holes, cracks in building/windows	
No insects/rodents	
No unrelated traffic/pedestrian flow	
Area secured behind closed doors	
Size of facility adequate	
Separate area for QA/QC sampling/testing	
Storage of packed and labeled goods awaiting shipment	
Special storage for special temperature/humidity requirements	
Necessary utilities in sufficient quality and quantity	
Adequate lighting and ventilation	

Checklist for personnel working in finished goods, storage and warehousing

Personnel	**Status**
Determine minimum number of personnel needed	
Position Description (PD) for each employee	
Chart key functions/personnel	
Identify basic qualification for each PD	
Identify special skills for each PD	
Identify key staff and delegate/assign responsibilities needed for proper functioning e.g. supervising/training/ maintenance.	
Develop training program	
Schedule periodic retraining	
Schedule periodic performance evaluations	

Checklist for equipment of finished goods, storage and warehousing

Equipment	**Status**
Dedicated equipment available for Lifting and transporting	
Special storage-constant room temperature and humidity	
Measuring/weighing/sampling	
Cleaning equipment	
Equipment in good working order	
Cleanliness	
Maintenance/lubrication according to schedule	
Calibration	
Validation	
SOP's	
Correct equipment available	
Equipment/ supplies/ manuals available to lubricate, calibrate, maintain, and repair	

Chapter VIII

PACKAGING

Chapter VIII: Packaging

Concepts and definitions

Packaging involves the sub-division of bulk finished product into packs that contain a sufficient quantity either for a course of treatment, for dispensing purposes or for retail sale.

The purpose of packaging is to

- Protect the product from damage, deterioration and contamination during storage and distribution.
- Identify the product, its origins and batch number.
- Give directions for use.
- Give mandatory and advisory warnings of hazards in use.
- Help with patient compliance.
- Where appropriate, present the product in a form that can be easily used by the patient.

It is essential that the process used for packaging is

- Properly designed.
- Shown to be capable of producing packages which comply in all respects with the finished product specifications.
- Comprehensively and formally defined.
- Carried out by properly trained personnel with adequate supervision.

And that

- Relevant stages in the packaging operation are checked and monitored.
- Samples of finished packs are inspected to ensure that they comply with the finished pack specifications.

Packaging practice

The following should be agreed, specified and documented in accordance with relevant company and legislative requirements prior to any packaging process being started:

- Sources and specifications of all packaging materials.
- The system for ordering, handling and approving all categories of packaging materials.
- Standards for the facilities and equipment to be used (in terms of construction and performance).
- Commissioning and qualification results as necessary for the facilities and packaging equipment.
- Master packaging instruction and method (detailing all materials to be used) written in clear and unambiguous language.
- Process validation, if required.
- The definition of a packaging batch.
- Acceptable ranges for process control parameters and operating conditions.
- In-process control and monitoring systems.
- Cleaning and inspection procedures for all packaging equipment

- Product inspection systems and standards.
- Systems for the control of printed material and overprinting of variable information (e.g. batch numbers and expiry dales).
- Standard operating procedures.
- Finished pack specifications.
- Storage systems and conditions to protect the integrity of the products at all stages of packaging.
- Systems for ensuring that adequate packaging records are completed, checked, and stored.
- System for ensuring that all personnel involved in the packaging operation are suitably qualified and adequately trained.
- Systems for ensuring safe working practices.

Packaging operation

The packaging operation for each product or product type will have its own requirements as specified in the master packaging instruction and method. Packaging should only be carried out in accordance with these formally approved procedures and methods. Details of the packaging operation must be recorded on the batch packaging record. Packaging lines are normally used for a variety of different products. Packaging of similar packages should not be in near areas. It is essential therefore that thorough checks are carried out on completion of each run and prior to the commencement of the next operation. These should ensure that:

- The packaging equipment and environment comply with that specified in the master packaging instruction and method and with appropriate GMP standards.
- The line clearance should be performed according to an appropriate checklist and recorded.
- The packaging line has been cleaned in accordance with specified procedures.
- There are no residual bulk products, containers, labels, cartons, leaflets or finished packs present.
- On-line printing and coding equipment has been set up correctly.
- The line is correctly identified with the name and batch number of the next batch to be packed.

Checks should be carried out to demonstrate adherence to the performance requirements of the packaging process. These include checks on:

- The weight, number or volume contained in the finished pack.
- The cleanliness of the primary containers.
- Freedom from defective items in the bulk product or in components that have been accepted on the basis of statistical sampling.
- Product, labels, canons, leaflets, line identification etc.
- Appearance and function of the pack.
- Adequacy of closures and seals.

- Function of checking systems (e.g. check-weighing units, barcode readers).

The checks described above should be carried out at the commencement of the packaging run and thereafter at set intervals. They are normally carried out by production personnel backed up by less frequent audit checks performed by quality control personal. On-line control of the product during packaging should include at least checks on:

- The general appearance of the packages.
- The completion of the packages.
- The use of the correct products and packaging materials.
- The correct overprinting.
- The correct functioning of line monitors.

Where automatic machines are used to check dimensions, weights, missing product labels, barcodes etc. test pieces should be used to check their correct operation. This should be done in accordance with written procedures and should be recorded. Where appropriate, statistical quality control methods should be used to control variables and attributes. Those most commonly used are concerned with fill weights and volumes and with batch assessment using standard sampling plans and tables.

Where the amount of packaging materials originally issued is found to be insufficient to complete the packaging run, additional quantities may be required. The issue of extra material should be

authorized by a formal procedure which specifies the same level of checking and documentation as required for the initial issue.

Excess overprinted packaging materials should be counted as far as is practical and be destroyed. The results of this count should be used to check that the correct quantity has been used. Unprinted items may be used either for further packaging operations (provided they satisfy the start-up checks) or returned to stock. In the latter case they should be counted as far as is practical, and checked by quality control before being returned to stock. Surplus product may be returned for re-use following similar procedures. Rejected product should either be destroyed or set aside for recovery of the active ingredient.

Occasionally, packaging materials and bulk products may be found to be unsatisfactory or isolated defective items picked out during packaging. It is important that these occurrences are recorded, reported and investigated to find their cause. The materials or products should be impounded or quarantined until their fate has been decided.

Where products are packaged in two separate stages, each stage should be regarded as a separate packaging operation with appropriate start-up checks, accountability of materials, supplementary documentation and records. It may be necessary to handle and store unlabelled packs. Where this happens, the part finished packs should be marked and the containers in which they are held labeled and stored in such away as to preserve batch integrity and allow them to be identified as regards product name, batch number, quantity and production stage.

Effective reconciliation of materials used in packaging operations provides assurance of product integrity. The most critical items in this respect are the product itself and printed packaging materials. Some methods of handling packaging components such as roll-feed labels are a benefit to product security but may themselves make exact reconciliation more difficult as a result of the problem of obtaining exact counts. In practice it is better to improve the security of materials storage and usage than expend effort on trying to achieve better but still incomplete reconciliation figures.

Repackaging of any kind should only be carried out in accordance with formally approved procedures and with the agreement of quality control. Non-standard and unforeseen circumstances should be notified to production management and to quality control immediately. This should be confirmed in writing promptly and the results of any follow-up action should be included in the batch packaging record.

On completion of packaging, the operators and supervisors involved should ensure that the batch packaging record is complete and check them for irregularities, mistakes and omissions. When packaging personnel have assured themselves that the records are satisfactory, the documents should be submitted to quality control for further review. On completion of the packaging operation, each batch should be either physically or procedurally quarantined, until quality control release and "qualified person" certification are complete.

Finalization of packaging

When the packaging is final it should be assured that packaging volume is in accordance with processing order. All packages should be put on pallets and be sure from the safety of the outer pack. It should be assured that batch no. and product name is written on all containers by a supervisor. Batch size should be recorded in a special record. If there is a difference between theoretical yield and actual yield it should be recorded in the special file, with reasons. All packaged goods are transferred to its special store. 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 returned printed materials are returned to stock.

All bad packed products should be returned to a responsible person to correct its pack or to damage it and all data must be recorded. Where any of the above systems and documents have a direct influence on finished product quality (e.g. control limits on fill weights), the limits, procedures and documents involved should be approved by the persons responsible for production and quality control. In addition, some aspects may need to be approved by the persons or units responsible for packaging development, engineering and safety. The master packaging instruction and standard operating procedures should be formally approved by the persons responsible for production and quality control prior to use.

Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines printing machine and other equipment are clean and free from any products,

materials, or documents previously used and not required for the current operation. Any utensils like combs or others must not be used to avoid hair fall or others in the package. No person should be ill. Inks, pastes, cleaning equipments should be kept in its package, with a label to identify the kind. Printed and embossed information on packaging materials should be distinct and resist to fading or erasing. Special care should be taken when cut labels are used and when overprinting is carried out off-line, and in hand packaging operations. On-line verification of all labels by automated electronic means can be helpful in preventing mix-up, but checks should be made to ensure that all used devices are operating correctly.

Issue of packaging materials

Packaging materials should be issued from stock in accordance with formal systems which ensure that they have been approved for use by quality control as complying with the relevant specifications. They are issued in rotation, the oldest being used first. Materials are used within their shelf-life. The correct quantity is issued. The containers used to transport packaging materials are adequately labeled to indicate the identity, quantity, batch number, code number and where appropriate, quality status of the contents. Primary packaging material and products are issued separately for each packaging run.

Records should be kept of each issue which include

- The name of the material.
- The code number.

- The batch or other reference number, if available.
- The amount issued.
- The personnel making the issue.
- The date of issue.

Checks on receipt into production

Each delivery of packaging materials received by the packaging unit should be checked to ensure that they are

- The materials as required by the packaging instructions.
- Correctly code numbered as specified in the packaging instructions.
- In a satisfactory condition in terms of cleanliness and freedom from damage.
- The quantity specified in the batch packaging documents.
- Approved by quality control.

These checks should be included in the batch packaging records along with the dates when the materials were received and the initials of the persons involved.

Overprinting

In many cases, printed components may be required to be overprinted with batch specific information i.e. Batch number, expiry date, date of manufacture etc. This may be carried out on the packaging line as part of the packaging operation or alternatively as a separate off-line activity. What ever the arrangements, overprinting

should only be carried out in accordance with the instructions contained in the batch packaging instruction, with the details being recorded in the batch packaging record. Checks must be carried out on the overprinting facilities used to ensure that

- The overprinting equipment and surrounding area are clear of all traces of the materials handled previously.
- The equipment has been set up correctly for the printing run to be carried out

These checks must be recorded in the batch records along with details of

- The numbers of items taken for overprinting.
- The number overprinted.
- The number of surplus unprinted items.
- The number of spoiled items.

An explanation of any discrepancy between the number of items issued and the number accounted for (outside agreed limits) should be given. Overprinted items should be stored in suitable containers which protect them from contamination and prevent mix-ups with other items. They should be clearly labeled with:

- The name and strength of the product on which they are to be used.
- Code number.
- Batch number (as overprinted).

- The packaging order number if different from the batch number.

Transfer into the packaging unit should be checked and recorded in the same way as packaging materials received from stores.

Preparation of other primary packaging materials

In some circumstances primary packaging materials (e.g. closures and containers) need to be cleaned prior to use. This may take place either as part of the packaging operation or separately as an off-line activity. In the latter case, it must be done according to a separate written procedure and the following included in the batch record:

- The date the operation was carried out.
- The name of the operator(s) carrying out the procedure.
- In-process control results.
- The quantities of components received from and delivered back to the packaging line.
- Losses and rejects.

Where these items are pre-printed with product or batch related information, care should be taken to avoid mix-ups. This will require similar checks to those described above for overprinted materials.

Checklist for premises of packaging and labeling

Facilities	**Status**
General cleanliness of area	
No leaks, holes, cracks in building/windows	
No insects/rodents/vermin	
No unrelated traffic/pedestrian flow	
Area secured behind closed doors	
Floors/walls covered with material to facilitate cleaning	
Size of facility adequate	
Separate area for Storage of approved incoming materials to be processed	
Storage of packed and labeled batches awaiting transfer to Warehouse area	
Special storage for special requirements	
Protected storage for labels before, during and after a labeling run	
Necessary utilities in sufficient quality and quantity	
Adequate lighting and ventilation	

Checklist for personnel working in packaging and labeling

Personnel	**Status**
Determine minimum number of personnel needed	
Position Description (PD) for each employee	
Chart key functions/personnel	
Identify basic qualification for each PD	
Identify special skills for each PD	
Identify key staff and delegate/assign responsibilities needed for proper functioning e.g. supervising/training/ maintenance.	
Develop training program	
Schedule periodic retraining	
Schedule periodic performance evaluations	

Checklist for equipment of packaging and labeling

Equipment	**Status**
Dedicated equipment available for Lifting and transporting	
Special storage-constant room temperature and humidity	
Measuring/weighing/sampling	
Cleaning equipment	
Packaging and labeling	
Sealable containers for storage/transfer of final dosage form batches to packaging and labeling area	
Equipment in good working order	
Cleanliness	
Maintenance/lubrication according to schedule	
Calibration	
Validation	
Correct equipment available	
Equipment/ supplies/ manuals available to lubricate, calibrate, maintain, and repair	

Chapter IX

DOCUMENTATION

Chapter IX: Documentation

Concepts and definitions

A document is the written procedures, instructions, requirements, registration files and others that to be needed in storage, procedures, manufacturing and quality control. Documentation is a prime necessity in quality assurance. Its purposes are to:

- Define the system of control
- Reduce the risk of error inherent in purely oral communication
- Insure that personnel are instructed in the details of, and follow the procedures concerned
- Permit investigation and tracing of defective products.

Good documentation constitutes an essential part of the quality assurance system, hence it helps in:

- Reducing the number of mistakes
- Finding the causes of poor quality
- Giving clear message on how work should be done
- Keeping records of how work was done
- Tracing which batches of materials were used in which batches of product and where the batches were delivered when dispatched from the factory

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

the manufacturing and marketing authorization dossiers. Documents should be approved, signed and dated by appropriate and authorized persons. Documents should have unambiguous contents; title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

Documents should be regularly reviewed and kept up-to date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents. Documents should not be handwritten; although, where documents require the entry of data, these entries may be made in clear, legible, indelible handwriting. Sufficient space should be provided for such entries. Data may be recorded by electronic data processing systems, photographic or other reliable means. Any alteration made to the entry on 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.

Types of documents

Three most important types of documents for quality assurance are

- **Specifications:** they give the standards of quality that can be measured and is used by quality department in deciding if a batch is passed or rejected.
- **Records:** Batch manufacturing records (processing and packaging) which reviewed by quality department. Batch

analysis records, completed and reviewed by quality department. Logs, used in production, engineering and quality department for records not directly related to a batch for e.g. cleaning, use of equipment, machine maintenance, etc.

- **Procedures:** Describe and give instruction on how work must be carried out. It can be special types of procedure, such as analytical methods or more general standard operating procedures (SOPs). SOPs must be used by anybody whose work can affect product quality, e.g. production, quality control department, warehouse and engineers.

1. Specifications

There should be appropriately authorized and dated specifications, including rests on identity, content, purity, and quality, for starting and packaging materials and finished products, where appropriate, they should also be available for intermediate or bulk products. Specifications for water, solvents and reagents used in production should be included.

i. Specifications for starting (raw) materials

Specifications for raw materials should include, if applicable

- The designated name and the internal code reference
- The reference, if any, to a pharmacopoeia monograph
- Name of final company
- The approved suppliers and, if possible, the original procedure of the products

- General specifications (color, taste, odor, form and dimension)
- Pharmacopoeia shape and strength
- Method of analysis
- Expiry date
- Storage conditions and precautions
- The maximum period of storage before re-examination
- Directions for sampling and testing or reference to procedures
- Qualitative and quantitative requirements with acceptance limits

Raw materials specifications certificate must embrace

- Trade name
- Scientific or chemical name
- Company trademark
- General specifications
- Origin certificates
- Storage requirements
- Method of analysis of raw materials including identification, purity tests, assays with their limits, physical and chemical characters, microbiological specifications with their limits. All these should be referred to the latest pharmacopoeia data, their addendum and references.
- Validity period and date of reanalysis.

Raw materials expiry date certificate

- Expiry date should be given to all raw materials with special attention to biological materials such as antibiotics, some vitamins, enzymes, hormones, vaccines and sera. After the termination of the expiry date these raw materials are destroyed.
- The other materials should be given validation date not more than 5 years. After that it can be re-analyzed and validation period may be prolonged according to the condition of the raw materials.

ii. Specifications for intermediate and bulk products

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

iii. Specifications for packaging materials

Specifications for packaging materials should include

- Company trade name
- Supplier trade name.
- General description (material, thickness, dimensions, color, touch)
- The required drawing

- Origin certificate
- Storage specifications and how to handle
- Inspection date of specifications

iv. Specifications for finished products

Specifications for finished products should include

- The designated name of the product and the code reference where applicable
- The formula
- A description of the pharmaceutical form and package details
- Directions for sampling and testing or a reference to procedure
- Qualitative and quantitative requirements, with acceptable limits
- The storage conditions and precautions, where applicable
- The shelf-life

2. Records

Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records and associated standard operating procedures should be retained for at least one year after the expiry date of the finished product. Records include batch manufacturing records (processing and packaging), batch analysis records and logs used in production, engineering and quality department.

i. Batch processing records

A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved manufacturing formula and processing instructions. The method of preparation of such records should be designed to avoid transcription errors. The record should carry the number of the batch being manufactured. Before any processing begins, there should be recorded checks that the equipment and work station are clear of previous products, documents or materials not required for the planned process, and that equipment is clean and suitable for use. During processing, the following information should be recorded at the time each action is taken and, after completion

- The name of the product
- Dates and times of commencement, of significant intermediate stages and of completion of production
- Name of the person responsible for each stage of production
- Initial of the operator of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g. weighing)
- The batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added)
- Any relevant processing operation or event and major equipment used

- A record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained
- The amount of product obtained at different and pertinent stages of manufacture (yield)
- Notes on special problems including details, with signed authorization, for any deviation from the manufacturing formula and processing instructions

ii. Batch packaging records

A batch packaging should carry the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained. There is a master filling method for batch packaging records including

- The name of the product dosage form and strength
- The date(s) and times of the packaging operations
- The name of the responsible person carrying out the packaging operation
- The initials of the operators of the different significant steps
- Records of checks for identity and conformity with the packaging instructions including the results of in-process controls
- Details of the packaging operations carried out, including references to equipment and the packaging lines used

Whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating and any

additional overprinting. Notes on any special problems including details for any deviation from the packaging instructions with written authorization by an appropriate person. The quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation.

iii. Batch analysis records

There must be record for test, analysis, approval, rejection of raw materials, in-process and final product. These records should be carefully kept and if they are booked, paper serial number must be given without tear off any paper. The record must include

- Date of test
- Material identification and its code number
- Supplier's name
- Batch number from quality control
- Batch size
- Date of batch size
- Method of analysis references
- Test results
- Comparison with standard product
- Name and signature of the analyst
- Analysis serial number

iv. Receipt records

The records of the receipts should include

- The name of the material on the delivery note and the containers
- Date of receipt and code of the material
- Supplier's name and, if possible, manufacturer's name
- Manufacturer's batch or reference number
- Total quantity and number of containers received
- Any relevant comment (e.g. state of the containers)

v. Distribution records

To facilitate effective recall, records of distribution should be kept showing the name and addresses of all persons to whom the manufacturer supplies a product.

vi. Stability studies record

It should include

- Product name
- Complete description of package
- Stability studies period
- Storage specification as temperature, relative humidity and light
- Stability studies results for each period
- The final results in comparison with the product original concentration

vii. Record for machine cleaning and maintenance

Maintenance: each machine card (m/c) must has its maintenance record to assure best operation, record for machine operation condition, maintenance procedure and record of all steps that have been done for its maintenance specially change of spare parts.

Cleaning: each m/c must has its cleaning method before and after operation mentioning the way of cleaning, tools used for this purpose, make a record to clarify application of cleaning method and the person concerned for cleaning and also concerned for cleaning inspection with correlation between m/c and record.

viii. Training record on GMP

Personnel training record on GMP should be available and include

- Training date
- The under training personnel during this period
- The training personnel
- Means and papers of training
- Schedule for training

ix. Self inspection record

Each self inspection record should mention the following

- Self inspection date
- Inspection documents
- Members of inspection

- Inspection results
- Copy of inspection list.

x. Record for the destruction of materials

The following requirements should be recorded

- Material name, batch number, and quantity
- Original supplier
- Method of destruction of materials
- Name and persons responsible for destruction
- Method of the refund materials record

xi. Quality control records

a. General requirements

There must be record for test, analysis, approval, rejection of raw materials, in-process and final product. These records should be carefully kept and if they are booked, paper serial number must be given without tear off any paper. The record must include

- Date of test
- Material identification and its code number
- Supplier's name
- Batch number from quality control
- Batch size
- Date of batch size

- Method of analysis references
- Test results
- Comparison with standard product
- Name and signature of the analyst
- Analysis serial number

b. Approved sampling method

Approved sampling method should include

- Sampling procedure
- Sampling devices
- Protective measures for sampling (including sampling uniform)
- Sector involved in sampling
- Time of sampling
- Specifications of sampling
- The containers from which the samples were taken

c. Certificate of analysis of pharmaceutical product

It should include

- Manufacturing site
- Manufacturing name and address
- Certificate number
- Product name (batch no., pharmaceutical shape, product strength, lot no of the raw materials, test limits, date of sampling)

- Result and their dales
- Notes
- Approval of product acceptance
- Signature of quality control manager

xii. Record for equipment standardization

To confirm good performance of the device (thermometers, spectrophotometers, pressure gauges, etc) periodical standardization of the device should be done and recorded in specific records for this purpose. This method must include:

- Time schedule for standardization
- Standard device
- Used measuring devices and detectors if any
- Standard procedure
- Any deviation record
- Name and signature of standardization operator

xiii. The method and record for cleaning the industrial area

A valid method should be available for cleaning of each industrial area and its record must include

- Area name
- Cleaning procedures in details

- Required materials and equipment for cleaning
- Time and schedule of cleaning

Cleaning schedule should be recorded clarifying the time needed for cleaning, zero balance time of cleaning agent stock and operator in charge.

xiv. Method and record for controlling the suspended particles in air and microbes in certain areas

This method is a must in certain areas and must include

- Working date
- Working area
- Results
- Required specifications
- Name and signature of operator in charge

xv. Method and record for destruction of insects and reptiles and others

Independent method for destruction of insects, reptiles and others should be available and include

- Work field
- The required work area
- Procedures in details with mentioning the required materials and measures

- Time schedule

Sectors, persons in charge for this work with the concerned records clarifying work date, the cleaning responsible company operation supervisors and used materials in each time.

xvi. Complaints records

A record should maintain of all complaints relating to product or packaging quality. This record should show the nature of the complaint, results of investigations and action taken. The record should be maintained in such a manner that significant recurrent complaints can be recognized and appropriate action taken.

3. Standard operating procedures (SOP's)

It is useful and probably necessary that there be a written standard operating procedure (SOP) describing how written procedures for production and process controls is initiated, reviewed and finalized. There shall be written procedures for procedures and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.

There should be standard operating procedures and records for the receipt of each delivery of starting materials and primary and printed packaging materials. There should be standard operating procedures for internal labeling, quarantine and storage of starting materials, packaging materials and other materials as appropriate.

Standard operating procedures should be available for each instrument and piece of equipment and placed in close proximity to the equipment. There should be standard operating procedures for sampling, which specify the person(s) authorized to take samples. The sampling instruction should include

- The method of sampling and the sampling plan
- The equipment to be used
- Any precautions to be observed to avoid contamination of the material or any deterioration in its quality
- The amount(s) of sample(s) to be taken
- Instructions for any required subdivision of the sample
- The type of sample containers to be used and whether they are for aseptic sampling or for normal sampling
- Any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material

Written procedures should be established and followed prescribing a system for reprocessing batches that do not conform to standards or specifications and the steps to be taken to insure that the reprocessed batches will conform to all established standards, specifications, and characteristics. There should be a standard operating procedure describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk, or finished product is identified with a specific batch number.

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. The standard operating procedure for batch numbering should assure that the same batch numbers will not be repeatedly used; this applies also to reprocessing. There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person. Records should be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary. Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for:

- Equipment assembly and validation
- Analytical apparatus and calibration
- Maintenance, cleaning, and sanitization
- Personnel matters including qualification, training, clothing, and hygiene
- Environmental monitoring
- Pest control
- Complaints
- Recalls

- Returns

Log books should be kept with major and critical equipment and should record, as appropriate, any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out. Written procedures should be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product, these procedures shall include, but are not necessarily limited to, the following:

- Assignment of responsibility for cleaning and maintaining equipment
- Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules
- A description in sufficient detail of the methods, equipment, materials used in cleaning and maintenance, operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance
- Removal or obliteration of previous batch identification
- Protection of clean equipment from contamination prior to use
- Inspection of equipment for cleanliness immediately before use

The procedures for sterile equipment are more involved and critical. In addition to the normal washing procedures, sterility must be ensured for certain containers and equipment used in manufacturing and filling operations. Terminal sterilization of the

product is not an acceptable substitute for proper cleanliness of manufacturing components, equipment, and utensils. *For sterile operations:*

- Containers used for holding sterile products must be sterilized and show the date of sterilization
- Components coming in contact with sterile products must be sterilized and show the date of sterilization
- Sterilized equipment or components should be used within 3 days of sterilization
- Sterilized equipment should be replaced between consecutive lot numbers of the same product to maintain the integrity of the control number
- Sterilization indicators should be used with equipment to show completion of the sterilization cycle

Written procedures describing the warehousing of drug products shall be established and followed, *they shall include:*

- Quarantine of drug products before release by quality control unit
- Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected

Written procedures shall be established, and followed, describing the distribution of drug products, *they shall include:*

- A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.
- A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary

Manufacturing formula and processing instructions

Formally authorized manufacturing formula and processing instructions should exist for each product and batch size to be manufactured. They are often combined in one document.

The manufacturing formula should include:

- The name of the product, with a product reference code relating to its specification.
- A description of the pharmaceutical form, strength of the product and batch size.
- A list of all starting materials to be used, with the amount of each, described using the designated name and a reference which is unique to that material, mention should be made of any substance that may disappear in the course of processing.
- A statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

The processing instructions should include:

- A statement of the processing location and the principal equipment to be used.

- The methods, or reference to the methods, to be used for preparing the critical equipment (e.g. cleaning, assembling, calibrating, sterilizing).
- Detailed stepwise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures).
- The instructions for any in-process controls with their limits.
- Where necessary, the requirements for bulk storage of the products; including the container, labeling and special storage conditions where applicable.
- Any special precautions to be observed.

Packaging instruction

There should be formally authorized packaging instructions for each product for pack size and type. These should normally include, or have a reference to, the following

- Name of the product.
- Description of its pharmaceutical form, and strength where applicable.
- The pack size expressed in terms of the number, weight or volume of the product in the final container.
- A complete list of all the packaging materials required for a standard batch size, including quantities, size and types, with the code or reference number relating to the specifications of each packaging material.

- Where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf-life of the product.
- Special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin.

There should be fixed procedures to refund a batch, it must include

- Refund field
- Refund threshold
- Refund regulation
- General protective measurements and what have done before
- Product name and batch no. and size
- Date of start and end of refund
- Refund reasons
- Refund quantity
- The source of refund goods
- Rectification of the subject
- The measurements have done for refund
- Final report including the report state

Complaints from pharmaceutical products

It is essential to find a way how to deal with pharmaceutical product complaint specially the serious side effects and should include

- Complaint definition or serious effect of the drug product
- Kind of complaints
- Dealing with complaints
- Rectification of complaints

In addition a record must be established and include the following

- Product name and batch no.
- Type of complaint
- Complaint sources
- Sample from the product
- Summary of complaint
- Test results
- Summary for complaint to follow its solution

The product refund should be through valid method include

- Product name
- Refund reasons
- How to refund

Refund record should be established and mention the following

- Information about product origin and method of storage
- Refund reasons
- Any tests can be done for the product
- The quantities to be destroyed

Product refund

The product recall from the market means the refund of its all packs from everywhere it is found, in case of valid record declare serious side effects which may affect patient's health. This refund can be done by manufacturer. The main aim of the refund is the rapid return back to prevent any damage of health care. The decision comes after the assurance of

- Production mistake
- Direction from authorities
- Direction from factory or supplier

Refund divisions

- Class (1) this indicates a very serious product that must be recalled within 24 hours.
- Class (2) this indicate not so serious product and must be recalled within 3 days.
- Class (3) product that must be returned back for different reasons.

Refund levels

Level (A) → Concerned with patient

Level (B) → Sale area

Level (C) →Auxiliary distributors

Level (D) → Main distributors

Products refund regulation

The induction of product refund is the responsibility of factory manager and also it is the responsibility of public pharmacists, factory, and government distribution areas. The Following precautions should be taken for product refund:

- Certain person should completely carry the responsibilities of products refund.
- Refund method should be determined. Communication ways, all the persons proposed to be contacted to prevent product distribution and its collection from government authority, pharmacists, physician distributors and even the public.

Preceding information for refund

- Batch no., name and pharmaceutical dosage form
- The risk if not refund
- Reasons for risk that lead to refund. (This only for government authority)
- Regulation of refund process
- The method used for contacting the person responsible for refund receipt

- Phone no., address, telex of pharmacy, clinics distributors, hospitals and others that have the product under refund

Refund procedures

- Refund class should be known (1, 2 or 3) to determine the time allowed for recall
- The use of rapid communication ways to contact areas of product under refund
- Determine the product quantity in the factory in order to not put it in use
- Refund receiving and holding in specified area
- A record for results should be established
- Determination of quantity and confirmation that the product is completely drawn from the market

Checklist for work procedures and sops of raw materials handling

Work procedures and SOP's	***Procedure being performed***	***SOP available***
Description of work/tasks done in Department		
Quarantine of incoming materials during testing		
Handling ingredients arriving in damaged containers		
Verifying ingredients with labels/purchase order, etc.		
Testing being done for identity strength, purity		
Special environment/temperature storing when required		
Storage of bagged materials		
Clean-up of spills/breakage		
Sampling without contamination		
Weighing/measuring materials to be transferred		
Ensuring critical steps checked by 2nd person		
Monitoring temperature/humidity control		
Cleaning storage areas according to schedule		
Monitoring shelf-life of raw materials		
Assuring only authorized personnel in work area		
Assuring personnel wearing protective clothing when appropriate		

Checklist for work procedures and sops of mixing and formulation

Work procedures and SOP's	*Procedure being performed*	*SOP available*
Description of work/tasks done in Department		
Receiving and storing approved raw materials in secure areas		
Verifying ingredients with label		
Special environment/temperature storage when required		
Sampling without contamination		
Documenting that QC/QA approved raw materials		
Weighing out raw materials to be mixed		
Assuring production/process/mixing steps performed according to master batch procedures and documented		
Assuring approved batch formulation, production, and control information is in the mixing area		
Master batch record available		
Records available		
Batches properly labeled		
Sampling procedures conducted properly		
Assuring mixed quantities equal to correct batch weight		
Assuring all intermediates, mixed batches, containers are properly labeled at all times		
Assuring and documenting correct mixing times		
Assuring correct intermediate samples, tests, and documentation for batch to have desired physical properties		

Work procedures and SOP's	***Procedure being performed***	***SOP available***
Ensuring critical steps checked by 2nd person		
Assuring QA/QC testing of intermediates		
Assuring proper handling and storage of intermediates		
Assuring final dosage form sampling and testing		
Assuring only authorized personnel in work area		
Ensuring only one batch in process per contaminant control zone		
Cleaning/lubricating/maintaining of equipment and install needed supplies according to schedule		
Clean-up area after each batch		
Clean-up of spills/breakage		
Assuring personnel wear appropriate clothing		

(Continued: Checklist for work procedures and SOPs of mixing and formulation)

Checklist for work procedures and sops of finished dosage form preparations

Work procedures and SOP's	***Procedure being performed***	***SOP available***
Description of work/tasks done in Department		
Receiving and storing approved materials in secure areas		
Verifying contents with labels		
Special environment/temperature storage when required		
Sampling without contamination		
Documenting that QC/QA has approved materials		
Weighing out and documenting materials to be prepared as dosage forms		
Ensuring only one batch in process per contaminant control zone		
Assuring approved batch formulation, production, and control information is in the dosage form preparation area		
Master batch record available		
Records available		
Batches property labeled		
Sampling procedures properly conducted		
Assuring all dosage form critical steps documented and checked by 2nd person		
Final dosage form production/processing conducted according to master batch and documented		
Filling processes		
Coating processes		

Work procedures and SOP's	***Procedure being performed***	***SOP available***
Sealing processes		
Assuring produced quantities equal to correct batch weight accounting for spillage, etc.		
Assuring all appropriate in-process tests are carried out		
Assuring all mixed batches and containers are properly labeled at all times		
Assuring correct storage and handling in sealed containers		
Correct QA/QC final dosage form testing including samples, tests, documentation for each batch to have desired chemical / physical properties an meet final approval standards		
Cleaning/lubricating/maintaining of equipment and install needed supplies according to schedule		
Assuring only authorized personnel in work area		
Clean-up area after each batch		
Clean-up of spills/breakage		
Assuring personnel wear appropriate clothing		

(Continued: Checklist for work procedures and SOPs of finished dosage form preparations)

Checklist for work procedures and sops of packaging and labeling

Work procedures and SOP's	*Procedure being performed*	*SOP available*
Description of work/tasks done in department		
Receiving and storing approved materials in secure areas		
Verifying contents with labels		
Special environment/temperature storage when required		
Sampling without contamination		
Documenting that QC/QA has approved materials		
Documenting/accounting for packaged and labeled materials		
Ensuring critical steps checked by 2nd person		
Ensuring only one batch in process per contaminant control zone		
Ensuring accountability and QC for labels		
Assuring approved batch formulation, production, and control information is in the packaging and labeling area		
Master batch record available		
Records available		
Batches properly labeled		
Sampling procedures properly conducted		
Assuring all packaging and labeling steps are performed according to master batch record, documented and checked by 2nd person		
Assuring produced quantities equal to correct batch weight accounting for spillage, etc		

Work procedures and SOP's	***Procedure being performed***	***SOP available***
Assuring all appropriate in-process tests are carried out		
Assuring all packaged containers are properly stored and properly labeled in sealed containers at all times		
QA/QC conducted according to schedule to assure correct samples, tests, documentation for batch to meet final approval standards		
Assuring that all labels are accounted for		
Cleaning/lubricating/maintaining of equipment and install needed supplies according to schedule		
Clean-up area after each batch		
Clean-up of spills/breakage		
Assuring only authorized personnel in work area		
Assuring personnel wear appropriate clothing		

(Continued: Checklist for work procedures and SOPs of packaging and labeling)

Checklist for work procedures and sops of quality assurance, production, process, and laboratory controls

Work procedures and SOP's	***Procedure being performed***	***SOP available***
Description of work/tasks done in department		
Storing raw materials, semi finished, and finished materials requiring special environments		
Sampling without contamination		
Documenting that QC/QA has approved testing materials for use		
Assuring most current approved batch formulation, production, and control information is available to the QC/QA staff		
Documenting QC/QA approval of Raw materials and intermediates		
Final dosage form		
Ensuring only one batch in process per contaminant control zone		
Assuring all steps in QC/QA process are documented and checked by 2nd person		
Documenting appropriate in process and final tests		
Documenting release of batch only after it complies with final approval standards		
Documenting that final batch has all the established physical, chemical, and microbiological properties		
Assuring correct batch weights at all points in the process		
Assuring all intermediates, mixed batches, dosage form, containers are properly labeled at all times		

Work procedures and SOP's	***Procedure being performed***	***SOP available***
Documenting all raw data in a sequentially paginated bound notebook with attachment of pertinent chromatograms, etc.		
Assuring all departments have documented procedures to follow when QA/QC tests show materials do not meet the required standards and have documented procedures for conducting investigations to determine the causes and make corrections		
Cleaning/lubricating/maintaining of equipment and install needed supplies according to schedule		
Cleaning-up areas after each QC/QA operation		
Clean-up of spills/breakage		
Assuring only authorized QC/QA personnel in QC/QA work area		
Assuring personnel wear appropriate clothing		

(Continued: Checklist for work procedures and SOPs of quality assurance, production, process, and laboratory controls)

Checklist for work procedures and sops of finished goods storage and warehousing

Work procedures and SOP's	***Procedure being performed***	***SOP available***
Description of work/tasks done in department		
Receiving, storing, accounting for approved finished goods in secure areas		
Verifying contents with labels		
Special environment storage when required		
Sampling without contamination		
Documenting that QC/QA has approved the finished goods		
Ensuring critical steps checked by 2nd person		
Ensuring correct product and batch production record labels attached to finished goods		
Accounting for and documenting finished goods going into or leaving storage		
Assuring that finished goods shipped match incoming order		
Cleaning/lubricating/maintaining of equipment and install needed supplies according to schedule		
Clean-up of spills/breakage		
Assuring only authorized personnel in work area		
Assuring periodic cleaning of warehouse		
Assuring personnel wear appropriate clothing		

EXAMPLES OF

STANDARD OPERATING PROCEDURES

(SOPs)

1. Standard operating procedure for calibration of analytical balance Mettler type AE200

1. Principle

The accurate weighing of a material is the basic fundamental procedure in proceeding analytical methods. To have an accurate weight, the following steps should be followed:

- A standard operation procedure should be applied for weighing materials
- The balance should be checked at certain frequency and calibrated in order to be sure that it is proceeding well all over the work hours.
- The balance should be labeled "un-repaired, under repair or out of order", if it has any defect and should not be used until this label is changed by the person responsible for calibration.

2. Equipment description

- Type AE 200
- Manufacturer: Mettler
- Range 205.00 g.
- Precision 0.0001 g.

3. Operation and calibration procedure

A. Internal calibration (daily check)

- Make absolutely sure that the balance is left connected to the power supply for at least 60 minutes before calibration.
- Press and hold the single control bar until "CAL" appears in the display, then release control bar. The display changes to "CAL ---" followed by "100.0000" then "CAL 0" blinks.
- Move calibration lever all the way back towards the front of the balance, the display changes to "---" followed by zero.

B. Operation procedure

- Level the balance by the leveling feet if necessary.
- Press lightly the "ON/OFF" button for a second to switch the display ON.
- Clear and clean the pan.
- Press "Tare" button.
- Load the sample to be weighed in the middle of the pan, close the balance door.
- After stability (the green dot in the display goes out), record the display reading.
- Not less than 50 mg should be weighed on the balance.
- There is a brief operating instruction which can be found on a card that swings out from underneath the balance housing.
- See manual for further information and details.

C. Calibration

i. Frequency: Monthly and after maintenance.

ii. A series of weights are weighed on the balance. If one weight or more is greater than the maximum tolerance allowed, the balance is calibrated by an internal calibration, and then all weights are checked again. If all weights are within specification limits, the balance is approved. In event that one or more weights are still out of specification limits, the balance is calibrated by an external calibration weight, then all weights are rechecked. If all weights are within specification limits, then the balance is approved. In event that one or more weights are still out of specification limit, the balances is labeled "out of order" and notify the person responsible for maintenance or the agent (for service).

iii. Put your result, comment and sign.

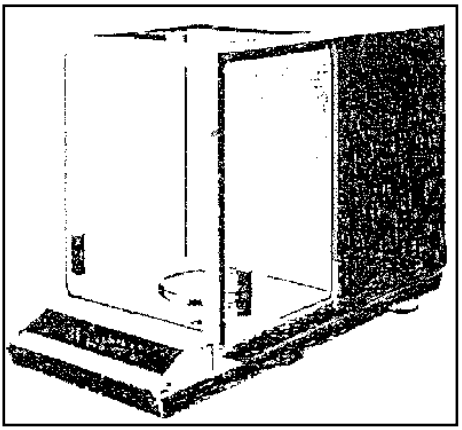
D. External calibration

- Make absolutely sure that the balance is left connected to the power supply for at least 60 minutes before calibration.
- Press and hold the single control bar until "CAL" appears in the display then release control bar. The display changes to "CAL ---" followed by "100.0000" then "CAL 0" blinks.
- Load an external weight of 100.0000 g. on the middle of the pan, the display changes to "----" followed by zero.

4. Maximum Tolerance (Specification limit)

Weight	Tolerance
10 mg	9.8000 - 10.2000 mg
50 mg	49.7000 - 50.3000 mg
500 mg	499.5000 - 500.5000 mg
5 g	4.9995 - 5.0005 g
50 g	49.9995 - 50.0005 g
100 g	99.999 - 100.0010 g

5. Equipment picture



6. Calibration material used

- A series of weights according to accuracy class F_1 comprising 10 mg, 50 mg, 500 mg, 5 g, 50 g and 100 g are used to check the balance before calibration adjustment.
- A 100.0000 g standard weight used for external calibration, supplied from the agent, when requested.

7. Notes

- Vibration, air currents, heat radiation and aggressive substances in the environment will affect not only the weighing result but also the balance integrity.
- After power connection, give the balance a warm-up time of 30 minutes.

8. References

Prepared by *Date*	*Approved by* *Date*

2. Standard operating procedure for sampling of raw and packaging materials

1. Principle

- Each delivery of materials should be visually checked on receipt for general condition, integrity of container(s), spoilage and possible deterioration. This physical inspection should be performed by the responsible warehouse personnel and recorded in the material Receiving Record.
- Sampling procedure must be carried out by QA responsible personnel and in the special sampling area in the warehouse (sampling booth).
- Care should be taken during sampling to guard against contamination of, or by, or causing deterioration to the material being sampled. Some particularly hazardous or potent materials may require special precautions.
- All sampling equipments that come in contact with the material must be dry and clean, and should be cleaned after each use and stored separately in the sampling area.
- Samples should be taken in such a manner that they are representative of the batches of material from which they are drawn and in a quantity at least twice that necessary to carry out all required tests, excluding samples for sterility and pyrogen testing.

- A sample of the raw material should be retained according to a suitable program and in a size sufficient to permit analytical re-examination.

- Stocks of materials should be inspected at intervals to ensure that the containers are properly closed, labeled and in a good storage condition. They should be re-sampled and submitted for retest at the intervals given in the material specification. Such re-sampling should be initiated by an effective documentary system.

2. Procedure

- Check each container label for correctness and clarity of the following information: item description, item number, vendor name, vendor lot number, weight of contents, total lot quantity received, manufacture date and expiry date whenever available and date of receipt to warehouse.

- Ensure that the container lids and surroundings are free from all potential sources of superficial contamination, (dust, wet, stain, etc), before opening, otherwise they should be wiped with dispensable cloth if necessary.

- After wearing the necessary protective clothing, remove the lid of the container and open the bag inside if any. Open one container at a time.

- Inspect the opened container visually for homogeneity of physical characteristics such as color, odor, particle size and absence of foreign particles.

- According to the sampling protocol take the required sample quantity using a suitable tool. Do not sample from the surface but scrape aside or whip and sample from the depth, then transfer to a suitable container.

- Reseal the inner bag, if any, then replace the lid and seal the container using the scotch sticker. Apply a label indicating the sample size, date of sampling and initials of the sampler.

- Each sample should bear a label with the same information as original container label in addition to the sample size and date.

- The quantity of sample drawn must be recorded in the receiving record.

- The details of inspection and sampling for each lot should be recorded in the inspection and sampling report.

3. Sampling tools and containers

- Sampling tools which are available for sampling include stainless steel scoops and thief scraper for powders, pipettes for liquids, stainless steel pipes for viscous liquids and stainless steel scrapers for waxy materials.

- These tools should be kept clean and dry, inspected periodically by the QA sampler and should not be used for dispensing or used by production personnel.

- Containers for keeping samples should be empty, clean and dry, preferably of glass with a tight closure, while those for sterility testing must be previously sterilized in an adequate manner by microbiology personnel.

4. Precautions

- Every container of materials intended for manufacturing of injectable product should normally be sampled aseptically and identified, either on receipt or before use in production.
- Samples for microbiological testing should be taken under aseptic conditions, e.g. under laminar flow, and as quickly as possible.
- Powders are sampled under the extraction hood (sampling booth), wearing the safety cloths, masks and gloves.
- Wear eye protection, respirator, gloves as well as overhead and laboratory coat while sampling potent drugs; irritant powders or toxic substances.
- Acids, caustic and inflammable liquids are sampled using a propipette and wearing gloves and masks.
- Materials that contain water of crystallization or photosensitive, should be sampled quickly and put in well tight dark containers e.g. $Na_2HPO_412H_2O$.
- Hygroscopic materials should be sampled in a dry area or under controlled humidity. The sample is taken quickly in a well tight container.

5. Sampling Protocol: Ref. MIL-STD-105D

A. Number of containers or units to be sampled per lot or batch

i. Active Raw Materials

No. of units			Open
2	-	15	2
16	-	25	3
26	-	90	5
91	-	150	8
151	&	over	13

ii. Inactive raw materials and primary packaging components

No. of containers units			Open & sample
2	-	8	2
9	-	15	3
16	-	25	5
26	-	50	8
51	-	90	13
91	-	150	20
151	-	280	32
281	-	500	50
501	-	1200	80
1201	-	3200	125
3201	-	10000	200
10001	-	35000	315
35001	-	150000	500
150001	-	500000	800
500001	&	over	1250

iii. Other packaging components

No. of units			Open & sample
2	-	15	2
16	-	50	3
51	-	150	5
151	-	500	8
501	-	3200	13
3201	-	35000	20
35001	-	500000	32
500001	&	over	50

B. The quantity of composite sample should be at least twice that needed to perform all tests, except for sterility and pyrogen testing, otherwise apply the following

Quantity Received	Sample Taken
Less than 250 g.	5-15 % of weight
250 – 5000 g.	2.5-10 % of weight
More than 5000 g.	125-260 g

Appendix I

MATERIAL RECEIVING RECORD

Item description			**Item number**	
Lot number	Vendor		Vendor lot number	
Receipt date	Mfg date	Exp date	PO: imported( ) local ( )	
Warehouse				
Comments	Status	Quantity	U/M	# of cont
	Received Rejected Physically Accepted			
	Sample Size		Taken by/date:	
Posted to RC Date	Posted By		Date	
Production comments – for packing items				
SIGNATURE DATE				
Quality				
Action Taken	Sign & date retest date		**Q. Ser. #**	
A Accepted			Expiry date	
Z Rejected			Potency %	
Quality comments				
SIGNATURE DATE				
Posted by				

Appendix II

RAW MATERIAL RETEST RECORD

Item description				**Item number**
Lot number		Vendor		Vendor lot number
Receipt date		Retest date		Quality serial number
Status	Quantity	U/M	Location	Signature/date
On Hand				
Sampled			Taken by	Date
Comments Signature		Date		

Test items	Specifications	Results

Analyst	R.M. Senior
Batch statement A Accepted Z Rejected	
N.B. Tick "/" in the Statement Box	
Comments Lab Manager Signature	Date
Posted by	Date

Appendix III

INSPECTION AND SAMPLING REPORT

Item description				Item number	
				Lot number	
I. Label Information					
Clarity	Ok/Not ok	---------	Lot no	Ok/Not ok	---------
Item descript	Ok/Not ok	---------	Wt of cont	Ok/Not ok	---------
Item no	Ok/Not ok	---------	Mfg date	Pres/Abs	---------
Vendor name	Ok/Not ok	---------	Exp date	Pres/Abs	---------
Vendor lot no.	Ok/Not ok	---------	Rece date	Pres/Abs	---------
II. General Condition					
A. Integrity of containers			B. Superficial contamination		
Tearing	Abs/Pres	---------	Dust & dirt	Abs/Pres	---------
Impairment	Abs/Pres	---------	Wet	Abs/Pres	---------
Sealing	Perf/Imperf	---------	Stain	Abs/Pres	---------
Rodent scars	Abs/Pres	---------	Others	---------	---------
III. Physical Characteristics Contents					
Status solid/liquid/ semi solid Uniformity: homogeneous /non-homogeneous Foreign particles: absent/present				Comment (if any)	
IV. Sampling Procedure					
Sample size solid/liquid/ semi solid Resealing & labeling of sampled containers: …….. Done Dispatching of samples to quality dept: …… Done Performed by Date / /					

Appendix IV

Sampling for identification purposes

The sampler must be aware of the possibility that containers of raw materials may be incorrectly labeled, and take steps to ensure that only the correct materials are used. Sampling and identity testing the contents of each container can provide the necessary assurance, but large deliveries in many containers can present practical and economic problems. In such circumstances it may be possible to relax the policy of identity testing the contents of every container and to apply our sampling protocol, if account is taken of the following

- The use to which the material is to be put. Every container of material intended for use as an ingredient of injectable products should normally be sampled and identified. In the light of further consideration, which follows, it may not be necessary to sample and identify each container of material for use in other product categories.
- The range of materials produced and handled by the original producer and any subsequent agents. The hazards of mislabeling are markedly reduced if the supplier deals only in one product or type of product. It is likely to be small if the supplier deals only in food products, greater if the supplier deals in a wide range of pharmaceutical materials, and probably greater still if the supplier deals in materials for both pharmaceutical and other industries. The broker who breaks and re-packages bulk martial may well represent a high level of risk.
- The status of the supplying company. If not well reputed or with problems from history, the sampled containers should be increased by two and each container is identified.

Prepared by **Date**	**Approved by** **Date**

3. Standard operating procedure for clearance and disinfecting of sampling booth area

1. Principle

- Sampling booth area should present a good appearance, be well maintained and must be kept in an orderly, clean and hygienic condition free from accumulated waste. It is a critical area.
- Sampling area as any area in the warehouse must be kept free of vermin, insects, birds and other pests.
- Control treatment should be carried out for cleaning according to this written procedure which does not contaminate the materials being held.
- Precautions must be taken to minimize the contamination of the area by dirty, damaged or unsuitable containers of raw materials which should not be accepted in this area for sampling. Also, considerations should be given to the provision of clean pallets for holding materials.
- In weighing process of sampling, and where raw materials containers are opened, all staff must wear protective clothing including, overheads, factory shoes, gloves, masks, etc. and must use appropriate safety equipment and use only new clean P.E. bags, clean glass or stainless steel containers for sampling.

2. Procedure

- Ensure that the sampling booth electricity is switched off before carrying out the cleaning procedure for sampling area.

- All materials and portable equipment must be removed outside the area.
- Clean up the settlement and spillages at the end of every working period using the vacuum cleaner to ensure that contamination is not carried outside the area.
- Clean the internal surfaces of booth to remove accumulated contamination using vacuum cleaner or clean towel.
- Clean the epoxy coated mild steel with warm water and mild detergent (liquid soap) or citric acid solution or sodium lauryl sulphate, then dry with clean towel.
- Tools of machines cleaned by using warm water and soap, then disinfected by using cotton wetted with alcohol 70% and dried.

3. Cleaning Frequency

- Cleaning procedure concerning sampling area must be carried out at the end of every working day.

Prepared by **Date**	**Approved by** **Date**

4. Standard operating procedure for operation of HI8564 portable thermohygrometer

1. Principle

a. Specifications

	RH	° C	° F
- Range	10 to 95% RH	0 to 60 °C	32 to 140 °F
- Resolution	0.1 % RH	0.1 °C	0.1 °F
- Accuracy	± 2 % RH	± 0.4 °C	± 0.8 °F

- Response time: 6 seconds for 95% accuracy
- By means of three trimmers housed in the probe calibration of the Relative Humidity and temperature is done.
- Display: A 4-digit LCD display plus symbols. Battery wear indicator.
- Power supply: One 9 V battery for 100 hours of continuous use.
- Operation conditions: Room temperature from 0 °C to + 50 °C, humidity 95% maximum.
- Optional accessories: HI7101 calibration kit.

b. General Description

The HI8564 portable thermohygrometer measures both temperature and relative humidity and is composed of a display panel and a probe connected by means of a spiral cable. A shock-resistant plastic box houses the display panel where the various measures are shown. It is also equipped with a keyboard for the selection of the various functions and an electronic circuit which converts the signals sent by the probe into digits. The probe contains

both the sensors and the electronic circuits necessary to transit the temperature and humidity readings in current which are then translated by the display panel. The probe must never come into contact with water or other liquids.

Battery housing: When the battery has almost run down and only a few hours of functioning remain, The "V" symbol will appear on the display to indicate that the battery must be replaced.

c. Temperature/Relative Humidity Role

It is very important to measure the temperature and humidity of the stores and this requires an absolute determination of the required conditions for warehousing of the different critical materials e.g. raw materials, cartons, etc. Portable thermohygrometer must be daily used and checked as early as possible and during the course of the day in different locations for each store. Every check also, must be recorded and initiated by the checker on the temperature/relative humidity record sheets and translate it on graphic drawing charts weekly concerning the main store. All registered records must be reported immediately to the warehouse supervisor/manager and then to the QA Manager.

2. Using the Instrument

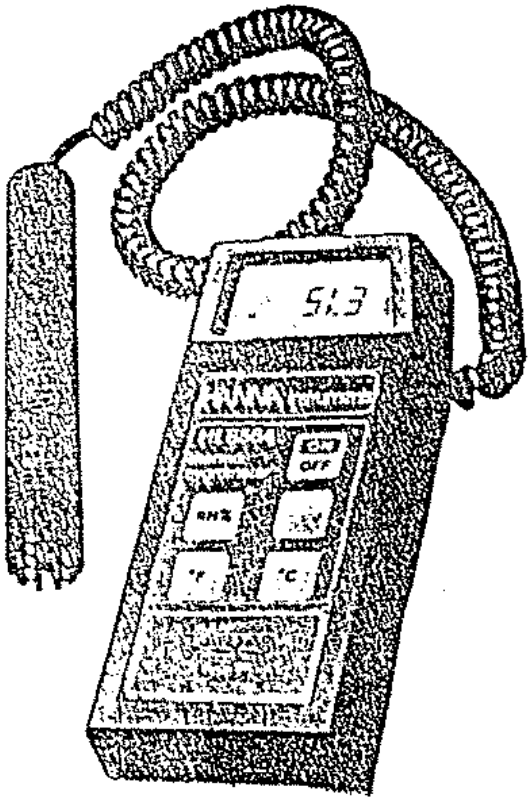
- In order to obtain a rapid response, the end of the humidity probe should be exposed to a current of air moving at more than 0.5 m/second. In the absence of air movement, the response can be speeded up by shaking the probe.
- If condensation causes drops of water to form upon the surface of the humidity sensors, the instrument must be turned OFF and

you must wait until this water has evaporated completely. In order to speed up the evaporation process, the humidity sensors may be exposed to a current of air.

- Whenever the humidity probe is to be used in dusty surroundings, the filter must be kept on at all times.
- Recording of temperature is in degrees centigrade and that of Relative Humidity in "RH-Percentage".
- There are many different stores with different levels or zones that must be checked daily for temperature and humidity as follows:

    1. Main store, three levels and two zones
    2. Receiving area, two zones (main entrance + waiting area)
    3. Reject store, one zone
    4. Officer's area, one zone
    5. Refrigerator, one zone
    6. Flammable store (outside the warehouse building), one zone
    7. Narcotic store, one zone
    8. Explosives store, one zone
    9. Central dispensing area, three zones (Weighing area + Batch assembly area + Printing House area)

HI 8564: Portable Thermo-hygrometer



Temperature / Relative humidity recording chart

Day	8 a.m.						2 p.m.						Checker	Supervisor Comment
	Level / Zone						Level / Zone							
	1		2		3		1		2		3			
	°C	.RH%	°C	.RH%	°C	.RH%	°C	.RH%	°C	.RH%	°C	.RH%		
1														
2														
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Prepared by **Date**	**Approved by** **Date**

5. Standard operating procedure for fumigation of the sterile area with formaldehyde gas

1. Principle

Fumigation of clean room environment using formaldehyde gas is done for the purpose of killing micro-organisms even in their spore forms, which may be found on walls, floor, and equipments or in the air condition (AC) system.

2. Scope of application and frequency

- When the routine biological monitoring indicate high microbial count in certain or whole of the area which resist the usual sanitizers in use.
- Fumigation is also indicated after major maintenance work in the area especially in the AC system.
- Normally fumigation should be affected monthly.

3. Precautions

Formaldehyde gas is a very irritant gas to lungs and eyes, avoid exposure to concentrations higher then 2 p.p.m.

Fumigation of the area must be affected while the area is empty from operators, product solutions, holding tanks or primary packaging materials

This procedure is applicable only when the other production departments are not working i.e. at the week-end.

4. Procedure

- Remove any packaging materials, solutions or holding tanks from the area
- Clean the area from dust or debris
- Rinse the floors and walls using water for injection and leave it wet
- Wear protection masks and eye protection glasses while dispensing the required amount of formalin solution
- Use a measuring cylinder to deliver 8 liters of formalin solution into 2 stainless steel bins each with 4 liters
- Place the filled stainless steel bin on electric heater with magnetic stirrer, in the corner near the sterilizing oven and the other in front of the changing room
- Adjust the timer clock of the power supply to the 2 electric heaters, so that to start the heater "ON" for the required time and lasts for 6 hours from the start
- Stop the AC to the area at the beginning of fumigation
- Re-start the AC system after 2 hours of fumigation while the fresh air supply is closed and leave for 5 minutes and then stop it again. This step is done to allow the formaldehyde gas to penetrate the A. C. ducts and filters.
- Close the doors of the area and seal the gaps around them using adhesive tape

- Run the AC system again when the timer clock indicates the end of fumigation time
- Re-start running the area at least after 10 hours of the fumigation process
- Make sure that the timer clock is in position "OFF" i.e. the power supply to the heaters is "OFF"
- Enter into the area and make sure that all the formalin liquid in the bin has been evaporated
- Close the containers and transfer to the air lock
- Test for the residual formaldehyde vapors in the environment this must not exceed 2 p.p.m.

Prepared by **Date**	**Approved by** **Date**

Chapter X

SELF INSPECTION AND QUALITY AUDITS

Chapter X: Self Inspection and Quality Audits

Concepts and objectives

The aim of self-inspection is to confirm that the GMP for pharmaceutical industries is applied properly inside the factory and that there is no defect in application with the suggestion of solutions enough to solve the problems. Inspection includes all manufacturing areas of the factory. Self inspection should follow a self inspection list approved by the GMP committee and must be classified into:

- Conform.
- Not conform.
- Report about (not conform).
- Report about if it is necessary to re-control any batch.

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 including personnel facilities

c. Maintenance of buildings and equipment

d. Storage of starting materials and finished products

e. Equipment

f. Production and in-process controls

g. Quality control

h. Documentation

i. Sanitation and hygiene

j. Validation and revalidation programmes

k. Calibration of instruments or measurement systems

l. Recall procedures

m. Complaints management

n. Labels control

o. Results of previous sell-inspections and any corrective steps taken

Self-inspection team

Management should appoint a self-inspection team from local staff who are expert in their own fields and familiar with GMP. The members of the team may be appointed from inside or outside the company. It consists of at least three persons (the number must be odd) they are chosen by factory manager (FM). The team must be chosen to cover different categories as follows:

- Quality control/quality assurance
- Production and engineer side
- Planning
- Public relations

Frequency of self-inspection

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

Self-inspection report

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

a. Self-inspection results

b. Evaluation and conclusions

c. Recommended corrective actions

Follow-up action

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

Quality audit

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

Supplier's audit

The quality control department should have responsibility together with other relevant departments for approving suppliers who

can reliably supply starting and packaging materials that meet established specifications. Before suppliers are approved and included in the specifications they should be evaluated. The evaluation should take into account a suppliers history and the nature of the materials to be supplier's. If an audit is required, it should determine the supplier’s ability to conform to GMP standards for active pharmaceutical ingredients.

Chapter XI

VALIDATION

Concepts and objectives

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 include:

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

Validation studies are an essential part in any quality assurance system and should be conducted in accordance with predefined protocols. A written report summarizing recorded results and conclusions should be prepared and stored. Processes and procedures should be established on the basis of a validation study and undergo periodic revalidation to ensure that they remain capable of achieving the intended results. Process validation enables production and quality control to have confidence that:

- Manufacturing processes will perform in a predictable manner
- There will be a high probability of test results on samples being representative of the entire production batch or run

- Process variables affecting quality have been identified and control limits set for them that will be effective and economic

Critical processes should be validated, prospectively or retrospectively. When any new master formula or method or preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be suitable to yield a product consistently of the required quality.

Any manufacturing process will involve a number of variables that affect product quality. It is the purpose of validation to explore this relationship, to establish the degree of variation that can be tolerated and the extent to which the process needs to be controlled in order to achieve acceptable quality product. It has been recommended that validation should be carried out at the extremes of these variables or under "worst case" conditions. Discretion must be exercised; otherwise it can lead to a large number of permutations of process conditions requiring validation. It is therefore logical to restrict variations and permutations of variations to:

- Those likely to yield product complying with the target and extreme values of specification limits
- Those that can reasonably be expected to be encountered
- Those that can be changed by human intervention or error
- Those that are known to affect important product characteristics and product quality

In theory, validation should only need to be carried out once for a given process in relation to a particular item of equipment. In practice when any aspect of the materials, process or plant known to affect quality is changed, revalidation should be carried out. The scope of the revalidation may well differ from the initial validation exercise as it is possible to use historical data accumulated both during the original validation and subsequently during routine production. The overall process of validation can be broken down into four distinct stages as follows:

- Commissioning - proving that the process plant/facility/utility installation is correct and functions in the absence of products.
- Qualification-demonstrates that each particular piece of equipment is capable of operating to pre-determined performance standards in the presence of placebo or product.
- Process validation-where the performance of the production process is evaluated in terms of compliance of the finished product with its specification and other relevant quality requirements and standards.
- Certification-formal documented acceptance of qualification, commissioning and validation results.

Process validation system

The process validation system should include the following key stages:

- Assessment of the need for validation work
- Preparation of a validation protocol

- Review and acceptance of the protocol by the person responsible for quality control
- Reporting of all the work carried out and the results obtained
- Review and acceptance (or otherwise) of the results and findings of the study
- Agreement on any changes needed to the process, and the in-process controls and monitoring to be performed routinely as part of the process
- Setting of the criteria for revalidation, maintenance, calibration, etc.

Process validation method

Assessment 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 processes 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.

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 form 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

As an example of prospective validation, for a granulated product the following steps should be considered:

- Typical process flow chart (fig. 1)
- Typical Variables and responses (table 1)
- Cause and effect diagram (fig. 2)

Figure 1. Typical process flow - granulated product

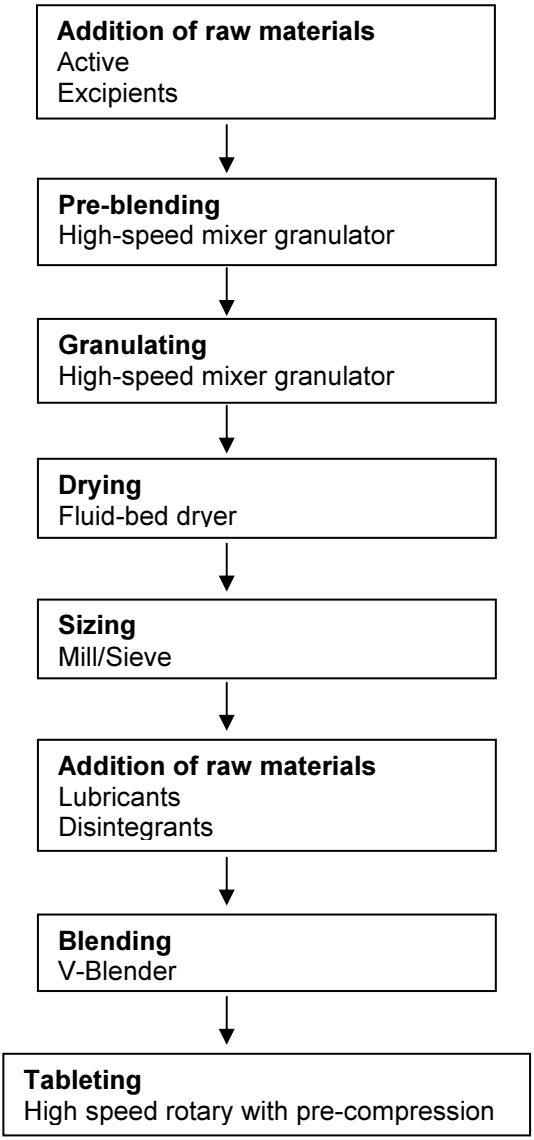
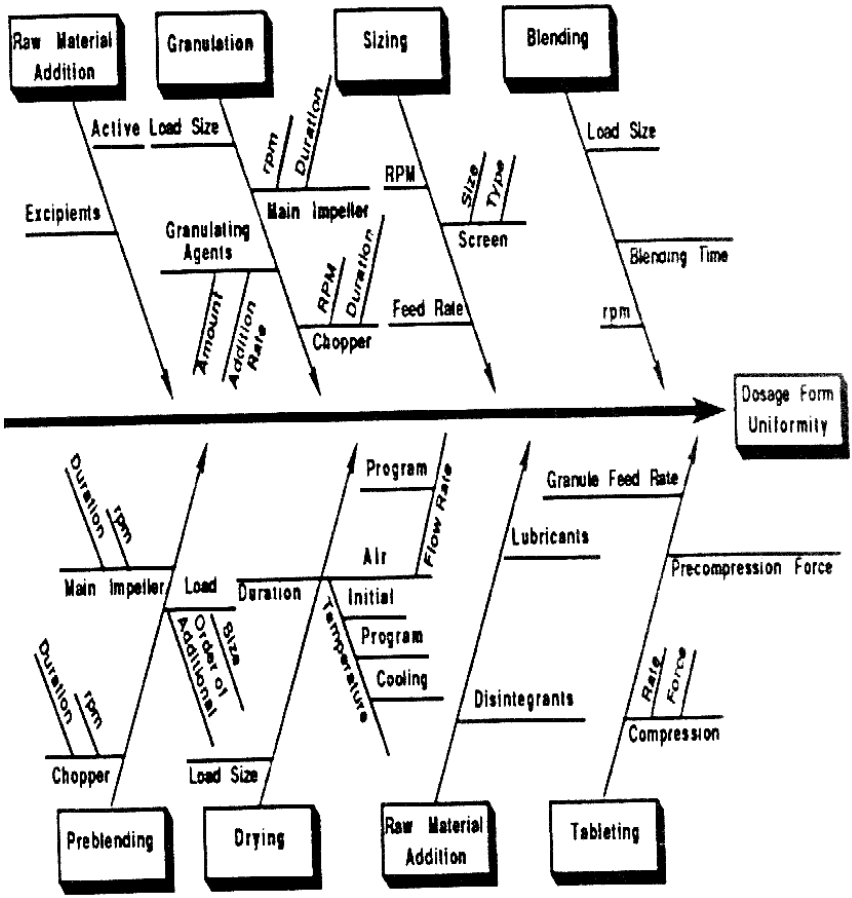


Table 1. Typical variables and responses - granulated product

Process Step	Control Variables	Measured Responses
Pre-blending	Blending Time RPM Load size Order of addition	Blend uniformity
Granulating	Load size Amount of granulating agent Solvent addition rate RPM Granulation Time	Density Yield
Drying	Initial temperature Load size Draying temperature program Air flow program Drying time Cooling time	Density Moisture content Yield
Sizing	Screen type Screen size Feed rate	Granule size distribution Loose density Packed density
Blending	Load size RPM Blending time	Blend uniformity Flow characteristics
Tableting	Compression rate Granule feed rate Pre-compression force Compression force	Weight variation Friability Hardness Thickness Disintegration time Dissolution Dosage form uniformity

Figure 2. Cause and effect diagram - granulated product



In theory, the number of process runs cairned out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. In practice, it may take some considerable time to accumulate full data. The validation protocol should also indicate the way in which the work is to be cairned out and how the data generated are to be analyzed and reported. Statistical methods may be of value in assessing the data generated. Review and acceptance of the validation protocol is an essential stage in ensuring that on completion the validation results will be acceptable. It should be cairned out by the person or organizational unit that is responsible for quality control.

Certification

Validation reports should give a comprehensive explanation of the work carried out and should include the values 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 to the sources used and where they can be found. Any work done in addition to that specified in the protocol or any deviations 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 work. In both cases, the review of 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 re-validation, 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.

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 to 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 processes by simulated processing and filling trials.

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. Figure 3 shows the method of selection of candidates for retrospective validation and table 2 illustrates the selected critical manufacturing steps quality-control release tests to be considered in a typical compressed tablet product.

Documentation

The validation process is incomplete without adequate documentation. It is essential therefore that the documents written in preparation for validation, the records of the work done, the results and the records of decisions made are retained on file for at least the same period of time as batch records. These should include:

- A record of the decision to carry out validation
- The validation protocol and a record of its approval
- Comprehensive records for each batch of product/placebo processed
- Environmental monitoring results, if appropriate

Figure 3. Selection of candidates for retrospective validation

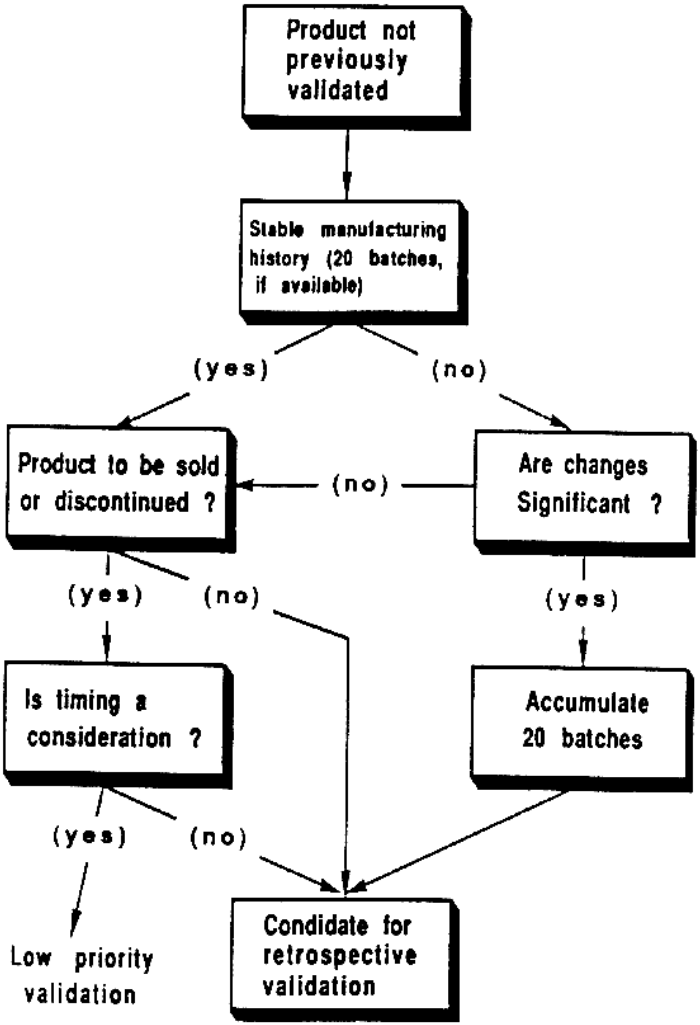


Table 2. Compressed tablets - selected critical manufacturing steps and quality control release tests

Processing Steps
Premix blending time
Oscillator screen size
Quality-Control Release Tests
Disintegration time
Hardness
Average tablet weight (ATW)
Assay
Dissolution

- Details of how the validation work was carried out, and results or at least summaries of results and observations
- Records of the evaluation of results and decisions to accept/reject the validation work by the person or unit responsible for quality control
- Records of proposals for suitable in-process controls, revalidation intervals, calibration, monitoring and maintenance

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.

Change control

Change control is another important element in any quality assurance system. Whilst there might not be procedures that are specifically titled "change control", systems should exist which ensure that proposed changes are identified, their significance evaluated and any consequent actions identified, evaluated and, where necessary implemented prior to the change being authorized. Change control is therefore closely linked to process validation. The

change control system should require formal notification of proposed changes in:

Materials	Components
Systems	Sources
Equipment	Methods
Conditions	Location
Specifications	Documentation

Relating to established processes and products, it can therefore be used to "trigger" validation work. Requests for and notifications of changes need to be considered either by a team which includes quality control or by the latter alone. The team should ensure that the validation system is followed as appropriate and also ensure that products made by processes subjected to changes are not automatically released for sale. Further to this, the change control system should ensure, by means of regular checks, that all notified or requested changes are satisfactorily completed, reported and validated.

Chapter XII

HAZARDOUS MATERIALS

Concepts and objectives

There are a number of potent chemical agents which cause special hazards to the health of employees who handle them. Examples of these agents are cytotoxic substances, certain steroids, cardiac glycosides, anti-coagulants, sensitizing agents, enzymes, prostaglandins and radioactive materials. When dealing with these substances, operating procedures need to ensure that the people involved are adequately protected from exposure. In many cases, these "employee protection" considerations make it more difficult to comply with good manufacturing practice.

An example of conflicting requirements is where health and safety considerations would dictate that the least number of people possible are exposed to a hazardous raw material whereas GMP requirements for check-weighing requires the presence of two Persons. Management must be aware of the potential for such conflict, anticipate or recognize it when it occurs, and implement solutions which satisfy both requirements. Possible ways in which these problems can be resolved include the use of:

- Closed circuit television for remote supervision and monitoring
- Enclosed manufacturing systems
- Remote handling techniques e.g. robotics
- Purpose built isolators
- Pressurized air suits
- Safety cabinets

- Segregated areas

Manufacturing Areas

Hazardous materials are normally handled in purpose-built units which, by virtue of their design, ensure that manufacturing activities are isolated from other operations and also provide adequate protection for the employees involved. Such units are normally only used for one product or for one category of product. The operation of these areas raises a number of problems, which demand special controls and procedures. Additional problems arise where hazardous products have to be handled under clean or aseptic conditions as there is likely to be a direct conflict in air handling systems needed to meet employee protection and good manufacturing practice requirements.

Sampling

Because of the need to minimize exposure to the smallest number of persons possible, it may be necessary for production personnel to sample active ingredients and finished products. Quality control must however ensure that the operators involved have sufficient training and knowledge so that a representative, homogeneous sample is taken.

Training

Special training is required both for personnel likely to be exposed to hazardous materials and those authorized to enter the areas where they are handled. This should cover both safe working practices and good manufacturing practice, together with training in

the use and handling of protective clothing and in other special procedures. A log which lists the trained personnel authorized to work with various categories of materials should be maintained.

Ventilation of areas where hazardous materials are handled

These areas are normally kept under negative pressure with respect both to the external environment and to adjacent areas in order to prevent emission of the materials being handled. A system should be established to verify and record that the differential pressure of the processing area is correct throughout the process cycle. Any air exhausted from the manufacturing areas to the external environment should be treated in order to remove all traces of active material. The environment in special manufacturing areas should be controlled in order to preserve the integrity of the product and provide acceptable working condition in terms of temperature and relative humidity.

Protective clothing

The handling of some classes of hazardous materials requires the use of totally enclosed protective suits which are provided with their own air supply. Where these are used, procedures are needed to cover:

- Entry and exit from the suit
- Decontamination and storage of suits when not in use
- Precautions for working in a protective suit i.e. indicator light or alarm bell when the air supply fails.

Enclosed suits restrict mobility and dexterity and, as a result, certain in-process controls may not be possible. Where this happens increased end-product testing may be required provided that the risks of exposure for laboratory staff are acceptable.

Waste disposal

Waste usually consists of disposable filters; dust from collector units or from suction cleaning systems and material used in manufacture. It should be handled using the same precautions required during production and the containers used for disposal should be cleaned externally before they leave the controlled area. All waste from areas where hazardous materials are handled should be packaged in well closed, sturdy containers marked with the appropriate warning labels. The most effective means of disposal is by incineration, if it is permitted.

Special systems may be necessary to deal with certain waste materials, washings from cleaning activities and other forms of effluent. This may involve inactivation or absorption of the active material and disposal by approved methods.

Employee exposure

The exposure of employees to hazardous materials should be limited by containment of the sources of emission, where this is not possible personal protection should be employed. In addition, exposure can be limited by restricting the time that each operator is allowed to work on a particular process and by using different operators according to a rotation. A log should be kept of time spent in controlled areas for each employee. Consideration should be

given to excluding certain categories of employee, who may be particularly at risk from exposure.

Environmental and personnel monitoring

Procedures should be carried out for environmental monitoring which involve both sampling at the point of "personal" exposure and static sampling within the area at specified points. "Personal" sampling involves an individual carrying a pump and sampling head within or attached to the protective clothing worn in the processing area. This should sample air within his/her breathing zone.

Results of personal and static area monitoring should be compared with available standards or in-house target levels and standards. It should be clearly specified what action is to be taken if the target or action limits are exceeded. In addition, appropriate physiological and medical checks of the personnel working in the area should be carried out. These may involve monitoring either blood or urine for levels of contaminants as well as general medical examination.

Maintenance

Difficulties may be experienced in carrying out maintenance in areas where hazardous materials are manufactured. In particular, care is needed when maintaining systems (such as ventilation) which may be located outside the manufacturing area but may still be contaminated with hazardous materials. Some of these problems may be overcome by the careful design of units requiring

maintenance e.g. sealed systems for the disposal of filter/dust extractor residues.

Chapter XIII

STABILITY

Chapter XIII: Stability

Concepts and objectives

Stability studies demonstrate that the necessary critical characteristics present at the time of production and release can be expected to be present when the dosage form is administered. If safety and efficacy values decline, stability studies provide information to determine when and under what conditions the product should be withdrawn from the market. The quality control department should evaluate the quality and stability of finished pharmaceutical products, and when necessary, of starting materials and intermediate products. The quality control department should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions. A written programme for ongoing stability determination should be developed and implemented to include elements such as:

- A complete description of the drug involved in the study
- The complete testing parameters and methods describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability
- Provision for the inclusion of a sufficient number of batches
- The testing schedule for each drug
- Provision of special storage conditions
- Provision for adequate sample retention and a summary of all data generated, including the evaluation and the conclusions of the study.

- A summary of all the data generated, including the evaluation and the conclusions of the study.

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

Purpose of stability testing

The main objectives of stability testing are:

- To select adequate (from the viewpoint of stability) formulations and container closure systems
- To determine shelf-life and storage conditions
- To substantiate the claimed shelf-life
- To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product

The type of stability studies depends on the different phases of drug and use:

In the development phase: Accelerated stability studies are used to predict the stability, shelf-life and storage condition of the final formulation. Real time studies have to be started for confirmation.

For the registration dossier: The results of stability studies from both accelerated and real time studies for the final dosage form in its final container and packaging should be submitted to the drug regulatory authority. Studies at the worldwide climate zone will be fruitful.

In the post-registration period: Real time stability studies as well as studies at the climatic zones II and III and worldwide are used to substantiate the expiry date and the storage conditions previously projected.

Stability data should be submitted when required. In the course of GMP inspection, their availability and validity are normally verified. The stability and quality of the dosage form on the market should be checked through a follow-up inspection and testing program

Design of stability studies

The design of the stability testing program needs to take into consideration the intended market and the climatic conditions of the area in which the drug product will be used. Four climatic zones can be distinguished for the purpose of worldwide stability testing as follows:

Zone	***Standard Strong Conditions***	
	Temperature	***Relative Humidity***
I. Temperate	21°C ± 2°C	45 % ± 5 %
II. Sub-Tropical & Mediterranean	25°C ± 2°C	60 % ± 5 %
III. Hot, Dry	30°C ± 2°C	35 % ± 5 %
IV. Hot, Humid	30°C ± 2°C	70 % ± 5 %

Temperature listed above is the mean kinetic temperature

In Egypt the climate, varies with seasons and place, roughly corresponding to climates of zones II and III round the year.

Test Samples

For registration purposes test samples are taken from three different batches prepared under conditions simulating production of the finished products in the market packages. Two batches are tested if the drug is known to be stable. For on-going studies batches from current production should be sampled in accordance with a predetermined schedule. The following approach may be suggested:

- One batch every other year may be tested for formulations considered to be stable, (otherwise one batch per year).
- One batch every 3-5 years may be tested for formulations when the stability profile has been established, unless a major product change has been made.

Types of stability studies and test conditions

Accelerated studies

Stress and acceleration tests are used to:

- Identify the weakness of an active ingredient or a formulation
- Make stability prediction
- Obtain information on extreme loading during transport

The storage temperatures used to test for chemical changes are within the range between 40 and 80 °C. It thus becomes possible to accelerate the rate of decomposition to such an extent that relevant results are available within three months on the basis of which stability predictions can be made applying the laws of reactions kinetics.

The temperatures are a continuation of those used for long-term testing. The temperature is increased in 10°C steps (21°C, 25°C, 30°C), 40°C, 50°C, 60°C, 70°C and 80°C. Which and how many of these are used depends on the problem under consideration and the dosage form. For a reliable stability prediction, however, at least three temperatures will be necessary. Low temperature (-15°C) freezer, (2-8°C) refrigerator, and freeze-thaw cycling should be used when necessary.

Humidity condition and effect of light should be taken in consideration. The storage conditions for stress testing for organoleptic and physico-chemical changes differ depending on the dosage form. Accelerated stability studies can be designed to simultaneously test the influence of several variables and with appropriate statistical methodology determine actions and interactions between variables. High correlation between the results obtained from accelerated stability testing and from long term shelf studies are necessary.

Solid dosage form

The samples are stored in open container. Until equilibrium is reached under the storages of long-term testing and two further frequently used stress conditions 21°C/45%, 25°C/60%, 30°C/70% or 40°C/75%.

Semi-solid dosage forms

Studies should be conducted at a temperature between 4°C and 40°C. Also between freeze and 25°C if cold storage is required.

Liquid dosage forms

≥10°C, lying down and upside down to test compatibility with closure Stability of reconstituted product during utilization period shall be determined.

The influence of humidity and temperature on chemical stability is tested by storing in parallel two samples of different initial moisture content in packaging materials impermeable to water vapor (e.g. glass container with twist-off closure) at temperatures between 40°C and 80°C.

ii. Climatic Zones Stability Testing

From the storage conditions, testing intervals and storage period, the following schemes have been derived for worldwide use.

Worldwide

Temp °C	RH%	storage period and testing intervals (months)						
		0	6	12	14	36	48	60
25	60	x	x	x	x	x	x	x
30	70		x	x	x	x	x	x

Number of Batches: 3 batches.

Container: It should be the same or simulate the actual packaging used for shipping and/or storage.

iii. Long term study (real-time studies)

Experimental storage conditions should be close to the projected actual storage conditions in the distribution system, as

practicable. As for the length of studies for registration purposes, results of at least 6 months studies should be available at the time of registration. It should be possible to submit the registration dossier before the end of this 6 months period.

Frequency of testing and evaluation of test results

In the development phase and for studies in support of an application for registration, a reasonable frequency of testing is considered to be a time period of:

For accelerated studies: 0, 1, 2, 3, and when appropriate 6 months.

For climatic zones: as indicated above

For real-time studies: 0, 3,6,12 months and beyond once a year.

For on-going studies: samples may be tested less frequently, e.g. at 6 months intervals for the confirmation of provisional shelf-life, or every 12 months for well established products.

Analytical method

Assay methods should be chosen to be stability indicating. Tests for related compounds or products of decomposition used should be validated to demonstrate that they are specific to the product being examined and are of adequate sensitivity, especially if proved to have potential toxicity. Test methods to prove the efficacy of additives, such as antimicrobial agents, should be foreseen to see if they remain effective and unchanged throughout the projected shelf-life. Stability regarding dissolution and sterility should be considered.

Recommended storage conditions

After evaluation of the stability, the product may be labeled with the following storage conditions:

Normal storage conditions: storage in dry, well ventilated premises at temperatures of 15-25°C or, depending on climatic conditions, up to 30°C. Extraneous odors, contamination, and intense light have to be excluded.

Defined Storage Conditions:

- Store up to 30°C
- Store up to 25°C
- Store between 2-8°C under refrigeration, no freezing
- Store below 8°C under refrigeration
- Store in a freeze at -5 to -20°C
- Store below -18 °C a deep freezing

General precautionary statement, such as "protect from light" and/or "store in a dry place", may be included.

Stability overage justification

The stability overage is acceptable only in limited cases and on grounds of scientific and practical justification.

New expiry date

Time-expired drugs should only be used in exceptional cases. The decision to utilize such products may be taken on a case-

by-case basis by a responsible national health authority only. In such cases, samples of these products have to be retested by stability-indicating method. When a decision is taken to use time-expired material, a new expiry date, well defined, and as limited as practicable has to be established.

List of less stable drug substance

The experimental conditions used to compile this list of less stable substances were the following: initial exposure for 30 days to air at 5°C and 100% humidity; if no degradation was demonstrable after this time. The temperature was raised to 70°C for a further period of 3-7 days. All other factors being equal, finished products containing the following substances require particular attention from the stability viewpoint.

Acetylsalicylic acid
Aminophylline
Amitriptyline hydrochloride
Ammonium chloride
Amphotericin B
Ampicillin sodium
Antimony sodium tartrate
Ampicillin trihydrate
Ascorbic acid

Bacitracin
Bacitracin zinc
Benzathine benzylpenicillin
Benzylpenicillin potassium
Benzylpenicillin sodium
Bephenuim hydroxynaphothoate

Calcium gluconate
Calcium para-aminosalicylate
Carbenicillin sodium
Cresol

Dapsone
Desamethaxone sodium phosphate
Dicloxacillin sodium (monohydrate)
Diethylcarbamazine dihydrogen citrate
Doxycycline hyclate

Emetine hydrochloride
Ephedrine
Ephedrine sulphate
Epinephrine
Epinephrine hydrogen tartrate
Ergocalciferol
Ergometrine hydrogen maleate
Ergotamine maleate
Ergotamine tartrate
Ethosuximide
Ethylmrphine hydrochloride

Cefalexin
Chloral hydrate
Chloramphenicol sodium succinate
Chloramphenicol hydrogen maleate
Chlorpromazine hydrochloride
Chlortetracylcine hydrochloride
Cloxacillin sodium (monohydrate)
Codeine phosphate
Colicalciferol
Coal tar

Ferrous sulphate
Fluphenazine decanoate
Fluphenazine hydrochloride
Formaldehyde solution

Gentamicin sulfate
Guanthidine sulfate

Hexylresorcinol
Hydralazine hydrochloride

Hydrocortisone sodium succinate
Hydroxocobalamin
Hyoscymaine sulfate

Imipramine hydrochloride
Ipecacuanha powder
Isoprenaline hydrochloride
Isoprenaline sulfate

Lidocaine hydrochloride

Melarsoprol
Mercuric oxide yellow
Mterifonate

Naloxone hydrochloride
Neomycin sulfate
Nystatin

Omeprazole
Orciprenaline sulfate
Oxytetracycline hydrochloride

Paromomycin sulfate
Penicillamine
Pethidine hydrochloride
Phenobarbital sodium
Phenoxymethylpenicillin
Phenoxymethylpenicillin calcium
Phenoxymethylpenicillin potassium
Phentolamine mesilate

Promazine hydrochloride
Promethazine hydrochloride
Pyridoxine hydrochloride

Quinine bisulfate
Quinine dihydrochloride

Retinol (Vitamin A)

Salbutamol sulfate
Senna leaf
Sliver nitrate
Sodium calcium edetate
Sodium lactate
Sodium nitrite
Sodium para-aminosalicylate
Sodium stibogluconate
Sulfacetmide sodium
Sulfadiazine sodium
Sulfamidine sodium
Suxamethonium chloride

Tetracaine hydrochloride
Tetracycline hydrochloride
Thiamine hydrochloride
Thiamine mononitrate
Thiopental sodium
Tolbutamide

Undecylenic acid

Phenylbutazone	**Warfarin sodium**
Pilocarpine hydrochloride	
Pilocarpine nitrate	
Procainamide hydrochloride	
Procaine benzylpenicillin	
Procaine hydrochloride	
Procarbazine hydrochloride	

List of substances resistant to degradation

The following substances proved to be resistant to degradation under the conditions of the test. It is important to emphasize that light was excluded, since some of these substances may be readily degradable under the influence of light.

Acetazolamide
Acriflavinium chloride
Ajmaline
Allopurinol
Aluminium diacetate
Aluminium hydroxide
Amikacin
Amiloride hydrochloride
Aminocaproic acid
Amobarbital
Atropine sulfate
Azathioprine

Barbital
Barium sulfate
Beclometasone dipropionate
Benzocaine
Benzoic acid
Benzyl benzoate
Betamethasone
Betamethasone valerate
Busulfan

Caffeine
Carbamazepine
Cetrimide
Charcoal, activated
Chloramphenicol
Chloramphenicol palmitate
Chloroquine phsosphate
Chlorothaizide
Chlortalidone
Clofazimine
Clofibrate
Clomifene citrate
Codeine monohydrate
Colchicine
Cyanocobalamine (Vit. B12)

Dexamthasone
Dexamthasone acetate
Diazepam
Diazoxide
Dicumarol
Diethylstilbestrol
Digitoxin
Digoxin
Dimercaprol
Diphenydramine hydrochloride
Disodium edetate
Dopamine hydrochloride

Ephedrine hydrochloride
Erythromycin
Erythromycin ethylsuccinate
Erythromycin stearate
Ethambutol hydrochloride
Ethinylestradiol

Fludrocortisone

Fludrocortisone acetate
Fluroscein sodium
Florouracil
Folic acid
Furosemide

Glibenclamide
Glucose
Griseofulvin

Haloperidol
Halothane
Hexobarbital
Hydrochlorthiazide
Hydrocortisone
Hydrocortisone acetate

Ibuprofen
Indomethacin
Iodine
Isoniazid

Lactic acid
Lactose
Levodopa
Lidocaine
Lindane
Lithium carbonate

Magnesium chloride
Magnesium oxide, heavy
Magnesium oxide, light
Mannitol
Mebendazole
Mepacrine hydrochloride
Methyldopa
Metclopramide hydrochloride
Metronidazole
Miconazole nitrate
Morphine hydrochloride

Neostigmine bromide
Neostigmine metilsulfate
Nicotinamide
Nicotinic acid
Nitrofurantoin
Norethisterone
Norethisterone acetate

Papaverine hydrochloride
Paracetamol
Phenacetin
Phenobarbital
Phenolphthalein
Phenytoin
Phenytoin sodium
Physostigmine salicylate
Piperazine adipate
Piperazine citrate
Potassium bromide
Potassium chloride
Potassium iodide
Prednisolone
Prednisolone acetate
Probenecid
Progesterone
Porpranolol hydrochloride
Propylthiouracil
Pyrazinamide
Pyridostigmine bromide

Quinidine sulfate
Quinine sulfate

Reserpine
Riboflavin

Rifampicin

Salicylic acid
Sodium bromide
Sodium chloride
Sodium fluoride
Sodium hydrogen carbonate
Sodium nitroprusside
Sodium salicylate
Sodium thiosulfate
Spironolactone
Streptomycin sulfate
Sucrose
Slufadiazine
Sulfadoxine
Sulfamethoxazole

Testosterone enantate
Testosterone propionate
Theobromide
Theophylline
Thioacetazone
Thiabendazole
Trimethadione
Trimethoprim

Zinc oxide
Zinc undecylenate

Content of stability reports

It is suggested that stability reports include the following information and data to facilitate decisions concerning the stability proposals.

General product information

- Name of drug substance and drug product or biological product
- Dosage form and strength, including formulation. The application should provide a table of specific formulations under study when more than one formulation has been studied.
- Labeling
- Composition, type, and size of container-closure

Specifications and test methodology information

- Physical, chemical, and microbiological characteristics and prior submission specifications
- Test methodology used for each sample tested
- Information on accuracy, precision, and suitability of the methodology
- For biological products, a description of the potency test(s) for measuring biological activity, including specifications for potency determination

Study design and study Conditions

- Description of the sampling plan, including:

- Batches and number selected

- Container-closures and number selected
- Number of dosage units selected and whether tests were conducted on individual units or on composites of individual units
- Sampling times
- Testing of drug or biological products for reconstitution at the time of dispensing (as directed on the labeling) as well as after they are reconstituted

- Expected duration of the study

- Conditions of storage of the product under study (temperature, humidity, light)

Stability data/information

- Lot number (research, pilot, production) and associated manufacturing date
- For antibiotic drug products, the age of the bulk active drug substance(s) used in manufacturing the lot
- Analytical data and source of each data point (e.g., lot, container, composite, etc). Pooled estimates may be submitted if individual data points are provided
- Summary of information on previous formulations obtained during product development. Summary should include other container-closures investigated.

Data analysis and conclusions

- Documentation of appropriate statistical methods and formulae used in the analysis.
- Evaluation of data, including calculations, statistical analysis, plots, or graphics.
- Results of statistical tests used in arriving at microbiological potency estimates.
- Proposed expiration dating period and its justification.
- Release specifications (establishment of acceptable minimum potency at the time of initial release for full expiration dating period to be warranted).

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