Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY
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MANILA, PHILIPPINES

September 29, 1999

ADMINISTRATIVE ORDER
No. 43 S. 1999

TO : ALL DRUG AND DEVICES MANUFACTURERS, TRADERS AND PARTIES CONCERNED

SUBJECT : CURRENT GOOD MANUFACTURING PRACTICE GUIDELINES FOR DRUGS.

The Bureau of Food and Drugs hereby adopts the 1st edition of Current Good Manufacturing Practice Guidelines and the specific GMP guidelines hereunder prescribed.

PART 1. GENERAL PROVISIONS

Section 1 Authority

This order is issued under the authority conferred upon the Secretary of Health by virtue of section 26(a) of RA 3720 as amended.

Section 2 Statement of Policies

2.1 Drugs shall be manufactured using methods, facilities and control procedures adequate to preserve their identity, strength, quality and purity.

2.2 License to manufacture drugs shall be issued only upon compliance with Current Good Manufacturing Practice guidelines.

2.3 Overall control is essential to ensure the manufacture of drugs conforming officially recognized standards of quality, efficacy and safety.

2.4 The qualities of drug products depend on the starting materials, production, quality control processes, building, equipment, and personnel involved and testing protocols.

Section 3 Statement of Objectives

This 1999 GMP guidelines is adopted to:

3.1 Prescribe standard guidelines in the manufacture of drug products

3.2 Ensure that no person or establishment shall manufacture drugs under substandard conditions.

Section 4 Definition of Terms

For the purpose of these guidelines, the following terms shall mean:

4.1 *Accuracy*

The nearest value obtained during measurement or analysis to the true value.

4.2 *Actual Yield*

The quantity that is actually produced at any phase of production of a particular drug product based on the initial input.

4.3 *Airlock*

An enclosed space with two or more doors, which is interposed between two or more rooms e.g. of different standard of cleanliness for the purpose of controlling the air flow between those rooms when they need to be entered. An airlock may be designed for and used by either people or materials; in the latter case it can be termed a “pass through hatch”. An airlock can also be the “anteroom” to a clean room in which sterile goods are handled.

4.4 *Approved Supplier*

A supplier of all components of finished products generally approved for use by the trade and accredited by the manufacturer based on a vendor rating which include but not limited to conformance to the company or compendium material specifications.

4.5 *Batch*

A quantity of drug product/device that is homogenous in character and quality produced during a given cycle of manufacture and from a specific manufacturing order.

4.6 *Batch Number*

A designation in numbers or letters or combination thereof that identifies the batch, and permits the tracing of the complete history of a batch, including all stages of its production, control and distribution.

4.7 *Biogenerator*

A contained system, such as a fermenter, into which biological agents are introduced together with other materials in order to effect their multiplication or their production of other substances by reaction with other materials. Biogenerators are generally equipped with devices for regulation, control connection, material addition and material withdrawal.

4.8 *Microbiological Agents*

Microbiological Agents including genetically engineered microorganisms, cell cultures, as well as endoparasites, whether pathogenic or not.

4.9 ***Blood***

Whole blood collected from a single donor and processed either for transfusion or further manufacturing.

4.10 ***Bulk Product***

Any processed material which has to undergo another process including packaging operation to become a finished product.

4.11 ***Calibration***

The operations carried out to determine the accuracy of measuring instruments, of "material measures" such as masses or gauges and of measurement standards.

4.12 ***Cell Bank System***

A system whereby successive batches of a product manufactured by culture in cells derived from the same master cell bank (see Master Cell Bank). The cell bank system is validated for a passage level or number of population doubling beyond that which was achieved during routine production.

4.13 ***Cell Culture***

The in-vitro growing of cells isolated from multicellular organisms.

4.14 ***Clean Area***

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

4.15 ***Compatibility Testing***

The in-vitro serological tests performed on donor and recipient blood samples to establish the serological matching of a donor's blood or blood components with that of a potential recipient.

4.16 ***Component***

Any material intended to be used for the manufacture of a product whether raw or packaging materials.

4.17 ***Contained Area***

An area constructed, operated and equipped with air-handling and filtration system in order to prevent contamination of the external environment by biological agents from within the area.

4.18 ***Contaminants***

Anything that cause contamination to the product.

4.19 ***Controlled Area***

An area constructed and operated to control the introduction of potential contamination (an air supply approximately class III may be appropriate), and the consequences of accidental release of living organisms. The level of control exercise shall reflect the nature of the organism employed in the process. The area shall be maintained at a pressure negative to the immediate external environment and allow for the efficient removal of small quantities of airborne contaminants.

4.20 ***Cross Contamination***

Contaminations of a starting, intermediate product or finished product.

4.21 ***Cryogenic Vessel***

A container designed to store liquefied gas at extremely low temperature.

4.22 ***Cylinder***

A container designed to store gas at a high pressure.

4.23 ***Date of Manufacture***

The date indicating the start of processing of every batch.

4.24 ***Dispensing***

The activity of weighing, counting or measuring and checking of starting materials and issuing these to the appropriate production personnel; details of the activity being duly and properly documented.

4.25 ***Documentation***

Written recording of all procedures, instructions and processes involved in the manufacture of drug products.

4.26 ***Drug Product***

Any substance or mixture of substances in finished dosage forms that is manufactured, offered for sale, or presented for use in (1) the treatment, mitigation, cure, prevention, or diagnosis of disease, abnormal physical state, or the symptoms thereof in man or animal; or (2) the restoration, correction or modification of organic functions in man or animal; regardless of whether it is in package form.

4.27 ***Device***

Instrument, apparatus, or contrivances, including their components, parts and accessories, intended (1) for use in the diagnosis, cure, mitigation, or prevention of disease in man and animals; or (2) to affect the structure or any function of the body of man or animal.

4.28 ***Expiration Date***

A date fixed for each individual batch on or before which the batch is expected to meet the standard specifications for quality, safety and efficacy.

4.29 ***Facilities***

For Blood Products: Any area used for the collection, processing, compatibility testing, storage or distribution of blood and blood components.

For Other Products (drugs, medical devices, bulk chemical material and others): This refers to the building, premises and equipment necessary in the manufacture of drugs.

4.30 ***Finished Product***

A product which has undergone all stages of manufacturing operations.

4.31 ***Good Manufacturing Practice (GMP)***

It is the system of quality assurance aimed at ensuring that products are consistently manufactured to a quality appropriate for their intended use. It is thus concerned with both manufacturing and quality control processes and procedures.

4.32 ***Infected (Man or Animal)***

Contaminated with extraneous biological agents and therefore capable of spreading infection.

4.33 ***In-Process Control***

Checks and tests instituted and carried out in the course of the manufacture of a drug to assure identity, strength, quality and purity.

4.34 ***Intermediate Product***

Any processed substance or mixture of substances which has to undergo one or more further stages of processing to become finished product.

4.35 ***Leukopheresis***

The process in which blood is extracted from the donor, a leukocyte concentrate is separated, and the remaining formed elements and residual plasma are returned to the donor.

4.36 ***Liquefied Gases***

Gases that, at the specified temperature and pressure, remain as a liquid in the cylinder.

4.37 ***Lot***

A batch or any portion of batch produced by a continuos process, an amount of drugs produced in a unit of time or quantity in a manner that assures its uniformity and in either case which is identified by a distinctive lot number and has uniform character and quality within specified limits.

4.38 ***Lot Number***

See batch number

4.39 ***Manifold***

Equipment or apparatus designed to enable one or more gas containers to be filled simultaneously from the same source.

4.40 ***Manufacture or Manufacturing***

The complete set of activities to produce a drug that comprise production and quality control from dispensing of materials to the release for distribution of the finished product.

4.41 ***Master Cell Bank***

A culture of fully characterized cells filled into containers in a single operation, processed together and stored to ensure uniformity and stability. A master cell bank is normally stored at -70oC or lower.

4.42 ***Master Seed Lot***

A culture of a microorganism distributed from a single bulk into containers in a single operation to ensure uniformity, stability and to prevent contamination.

4.43 ***Packaging***

The process of packing which is that part of the production cycle applied to a bulk product to obtain the finished product.

4.44 ***Packaging Material***

Any material used in the packaging of a bulk product to obtain the finished product.

4.45 ***Plasma (for further manufacture)***

The liquid portion of blood separated and used as material to prepare another product.

4.46 ***Plasmapheresis***

The process in which blood is extracted from the donor, the plasma is separated from the formed elements and at least the red blood cells are returned to the donor.

4.47 ***Plateletpheresis***

The process in which blood is extracted from the donor, the platelet concentrate is separated, and the remaining formed elements and residual plasma are returned to the donor.

4.48 ***Precision (in analytical assay and method)***

The degree of variation between individual test results when the method is used separately to different samples drawn from the same batch of material. This will include variation between analysts, between days, between tests on the same prepared extract of a given sample, between different extracts and between laboratories conducting the same test. It is normally divided into two types:

- Repeatability (within laboratory), and

- Reproducibility (between laboratories).

4.49 ***Primary Containment***

A system of containment that prevents the dispersal of a biological agent into the immediate working environment. It involves the employment of closed containers or safety biological cabinets accompanied with secure operating procedures.

4.50 ***Procedures***

Description of the operations to be executed, the precautions to be implemented directly or indirectly related to the manufacture of a drug.

4.51 ***Processing***

The part of production cycle starting from weighing of raw materials to finished product.

4.52 ***Processing of Blood***

Any process employed after collection and before computability testing of blood. It includes the identification of a unit of donor blood, the preparation of components from such unit of donor blood, serological testing, labeling and associated record keeping.

4.53 ***Production***

All operations starting from dispensing of materials to processing, packaging, to finished product.

4.54 ***Quality Control***

All control measures taken designed to ensure that finished products consistently conform to established specification of identity, strength, purity and quality.

4.55 ***Quarantine***

An act of holding off a material for use, or a product for packaging or distribution by physically setting it apart or by system duly validated, pending a decision on release or rejection.

4.56 ***Raw Material***

All substances whether active or excipients that are employed in the processing of a finished product.

4.57 ***Reconciliation***

A resolution between the theoretical and actual yield.

4.58 ***Recovery***

The incorporation of all or part of previous batches with the required quality into another batch at a defined step of production.

4.59 ***Rejected***

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

4.60 ***Released or Passed***

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

4.61 ***Representative Sample***

A sample representing the lot, the batch, or the total amount of materials based on a sampling plan.

4.62 ***Reprocessing***

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

4.63 ***Returned Product***

Any finished product which is already in distribution and sent back to the manufacturer or distributor due to complaint, damage, expiration, validity or

other reasons such as the condition of the container or package which may cast doubt on the product identity, quality, strength and safety.

4.64 ***Sanitation***

All measures taken to assure suitable or adequate environmental conditions in compliance to GMP.

4.65 ***Secondary Containment***

Secondary containment is a system of containment that prevents the dispersal of a biological agent into the external environment or into other working areas. It involves the use of rooms with specially designed air handling, the existence of air locks and/or sterilizers for the exit of material. It may add to the effectiveness of primary containment (see Primary Containment).

4.66 ***Seed Lot System***

A seed lot system is a system where successive batches of product are derived from the same master seed lot at a given passage level.

4.67 ***Specification of Material***

A description of starting material, intermediate, bulk or finished product in terms of its chemical, physical and microbiological characteristics, if any. A specification shall include descriptive and or numerical clauses stating standards and tolerated deviations, whenever applicable.

4.68 ***Starting Materials***

Raw materials used in the production of a finished product (drugs).

4.69 ***Sterile Room or Sterile Area***

A room or area of defined environmental condition with controlled particulate and microbial contamination, constructed, equipped and used to eliminate the introduction, generation or retention of contaminants.

4.70 ***Sterilization***

Inactivation or reduction to an acceptable level of all viable microorganisms by a suitable process.

4.71 ***Theoretical Yield***

The quantity that is expected or planned to be obtained at any phase of production of a particular product, based on the quantity of components to be used.

4.72 ***Unit (of Blood)***

The volume of blood or one of its components in a suitable volume of anticoagulant obtained from a single collection of blood.

4.73 ***Validation***

The process of confirming by recognized appropriate means or manner, that any material, process, procedure, activity, system, equipment or mechanics used in production and control consistently achieved the desired results.

4.74 ***Working Cell Bank***

A culture of cell derived from the master cell bank and intended for use in the preparation of production of cell cultures and normally stored at - 70OC or lower.

4.75 ***Working Seed Lot***

A culture of microorganism derived from the master seed lot and intended for use in production.

4.76 ***Worst Case***

A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when, compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

PART 2. BASIC GMP GUIDELINES

Section 1 *PERSONNEL*

There shall be an adequate number of personnel at all levels having knowledge, skills and capabilities relevant to their assigned functions, in good mental and physical health to be able to execute their duties.

1.1 ***Organization, Qualification and Responsibilities***

1.1.1 The organizational structure of the company shall be such that the production and the quality assurance are headed by different managers, neither of whom shall be responsible to the other. Each shall be given full authority and facilities necessary to execute his/her duties effectively. Neither shall have any interests outside the manufacturer's organization that prevent or restrict their dedication to the assigned responsibilities or which may be considered to entail a conflict of interest.

1.1.2 The production manager shall be a PRC registered qualified pharmacist or any other related profession. He/she shall be adequately trained and shall posses good practical experience in the

field of pharmaceutical manufacture and managerial skill, which enable him/her to perform his/her function effectively. The production manager shall have full authority and responsibility to manage production of drug products.

1.1.3 The quality control manager shall be a PRC registered qualified pharmacist or any other related profession. He/she shall have adequate training and practical experience that will enable him/her to perform his/her function effectively. The quality assurance manager shall have full authority and responsibility in all quality control processes such as establishment, verification and implementation of all quality control procedures. He/she shall have the sole authority to approve starting materials, intermediates, bulk and finished products that meet the specification or to reject those which do not conform to the relevant specification or which are not manufactured in accordance with the approved procedures.

1.1.4 The quality assurance manager shall clearly define the field of work and the method of delegating responsibilities in his/her absence.

1.1.5 The quality assurance manager shall have personal and professional responsibility for ensuring that various checks and tests have been carried out. The details of this work may be delegated to an appropriately trained and experienced staff who would endorse their work. Finally, the quality assurance manager has to be satisfied directly by the proper operation of quality systems that include appropriate approvals, audits, self-inspections and spot checks that the production and testing have complied with relevant requirements.

1.1.6 The production manager and the quality assurance manager are jointly responsible to establish for the quality, strength, purity and efficacy of the finished products.

1.1.7 To support and assist the key personnel, an adequate number of qualified personnel should be available in the production and quality assurance. Each personnel shall be adequately trained with their respective assignment.

1.1.8 The duties and responsibilities of all employees shall be clearly defined, well understood and shall be within his/her capacity to perform to ensure quality products.

1.2 ***Training***

1.2.1 All employees who are directly and indirectly engaged in the manufacturing activities shall be trained in the particular operations that the employees perform in accordance with the principles of Current Good Manufacturing Practice.

1.2.2 Training shall be conducted by qualified individuals. Special attention shall be given to training of personnel working in sterile and clean areas or with highly potent, toxic or sensitizing materials.

1.2.3 Training in Current Good Manufacturing Practice shall be on a continuing basis and with adequate frequency to assure that employees remain familiar with the Current Good Manufacturing Practice requirements relevant to their functions.

1.2.4 Training in Current Good Manufacturing Practice shall be in accordance with written program approved by the production manager and the quality assurance manager.

1.2.5 Records of personnel training in Current Good Manufacturing Practice shall be maintained and the effectiveness of training programs shall be assessed periodically.

1.2.6 After training, the consequential employees' performance shall be appraised to determine their capability to meet the qualification requirement for the jobs.

Section 2 *PREMISES*

The premises for manufacturing shall be of suitable size, design, construction and location to facilitate proper operation, cleaning and maintenance. The individual working areas shall be adequate so that any risk of confusion, cross-contamination and other mistakes that will adversely affect the quality of drugs and devices will be avoided.

2.1 *Location, Construction, Design & Lay-out*

2.1.1 Premises shall be so located and protected against contamination from the environment.

2.1.2 Premises shall be constructed and maintained to protect against weather, flood, ground seepage and the access and harboring of vermin, rodents, birds, insects or other animals.

2.1.3 In determining the design and lay-out of premises, consideration should be paid to:

2.1.3.1 the compatibility of other manufacturing operations that may be carried out in the same or adjacent premises

2.1.3.2 allow the production to take place in areas connected in a logical order according to the sequence of the operations and to the requisite cleanliness levels

2.1.3.3 the adequacy of the working space, which shall allow orderly and logical placement of equipment and materials to suit the operation, efficient flow of work, effective communication and supervision to avoid crowding and disorder

2.1.3.4 avoid the use of production areas as a general traffic for personnel or materials or for storage other than the materials in process.

2.1.4 The layout of rooms, corridors, and spaces shall provide for logical movements of materials and personnel with minimal traffic for operations to be carried out in defined areas and to avoid cross contamination. The design and layout of premises shall fulfill the following requirements:

2.1.4.1 the risk of mix-up between different drugs or their components, the possibility of cross-contamination by other drugs or substances and the risk of omission of any production step shall be prevented

2.1.4.2 penicillins shall be produced only in separate buildings, with separate air handling facilities dedicated to these products using dedicated equipment, including dedicated packaging lines.

2.1.4.3 cephalosporins shall be produced in separate buildings, with separate air handling facilities dedicated to these products using dedicated equipment, including dedicated packaging lines

2.1.4.4 cross contamination of products by live biologicals, or by drug products, such as certain steroids or cytotoxic agents which in trace amounts may produce physiological effects should be prevented by the following methods:

2.1.4.4.1 carrying out production operations in separate buildings or adequately isolating the operations by total enclosure or by making successive batches in the same or in dedicated equipment followed by validated cleaning procedures and where appropriate, fumigation

2.1.4.4.2 controlling airborne contaminants by the use of an appropriate air pressure differential in processing areas and adequate exhaust systems and filters, together with control of recirculated air

2.1.4.4.3 the setting and shielding of production equipment, and wherever possible, the use of equipment solely for one type of drug/product;

2.1.4.4.4 containment of contaminant-transfer by means of airlocks, clothing change and decontamination of containers and other articles prior to their removal from the isolated area

2.1.4.4.5 separate cleaning area for contaminated clothing

2.1.4.4.6 periodic testing of the environment around the production areas for the presence of the therapeutic substance being processed and

2.1.4.4.7 validation of cleaning procedures.

2.1.5 In all manufacturing rooms (processing and packaging), air supply and air exhaust points shall not be so close or so disposed as to restrict or negate the supply of clean air to worksites and or movement of product dust or other contaminants away from worksites. The airflow pattern within the facility and each manufacturing area and the throughput rate of air shall be selected to afford adequate protection to the products and personnel.

A plan of the building(s) showing air handling facilities including key air handling equipment and showing air quality standards, flow rates, proportions re-circulated and relative air pressures shall be made available for inspection.

2.1.6 Air handling facilities for the production of cytotoxins shall be appropriate. The anteroom should operate at a positive pressure relative to the processing area but negative or lower pressure relative to the outside or adjacent room.

2.1.7 The processing of materials for drug products shall be separated from the production of non-drug products.

2.1.8 Separate space for:

2.1.8.1 Cleaning mobile equipment

2.1.8.2 Storage of cleaning materials

2.1.9 Locker/gowning room shall be directly connected to but separated from processing areas.

2.1.10 Toilets should not be opened directly to production areas and shall have adequate supply of water and ventilation.

2.1.11 Experimental animals shall be housed in a separate building.[Refer to Annex on Biological Products for further details on Animal Quarantine and Care]

2.1.12 Defined areas for the following operations are required:

2.1.12.1 gowning/change rooms for all personnel

2.1.12.2 receiving of starting materials

2.1.12.3 incoming goods quarantine

2.1.12.4 sampling room for sampling of deliveries of starting materials

2.1.12.5 storage for approved materials (chemical & packaging)

2.1.12.6 storage of reject materials

2.1.12.7 laboratories

2.1.12.8 weighing / dispensing of materials

2.1.12.9 processing operations

2.1.12.10 equipment washing

2.1.12.11 storage of cleaned, idle/non-functional equipment

2.1.12.12 major repair and maintenance activities

2.1.12.13 storage of cleaning tools and supplies

2.1.12.14 staging/storage of bulk products

2.1.12.15 packaging / labeling operations

2.1.12.16 quarantine storage for finished products

2.1.12.17 storage for approved of finished products and

2.1.12.18 distribution center

2.1.12.19 cafeteria

2.1.12.20 process water treatment

2.1.13 Interior surfaces (walls, floors and ceilings) shall be smooth, free from cracks and open joints, shall not retain or shed particulate matter, shall permit easy cleaning and disinfecting. The floor in processing areas shall be made of impervious materials, laid to an even surface, shall allow prompt and efficient removal of any spillage. Walls shall be of impervious and washable surface. The coving of junctions between walls, floors and ceilings in critical areas is necessary.

2.1.14 Drains shall be of adequate size with trapped gullies. Open channels shall be avoided where possible, but if required, they shall be shallow enough to facilitate cleaning and disinfecting.

2.1.15 Air intakes and exhausts, and associated pipework and ducting shall be installed in a way that will avoid product contamination.

2.1.16 Production areas shall be effectively lit and ventilated with air control facilities (including temperature, humidity and filtration), appropriate both to the products handled, to the operation undertaken within them and to the external environment. [refer to section 2.1.5, 2.1.6]

2.1.17 Pipework, light fittings, ventilation points and other services in production areas shall be installed in a way that will have cleanable recesses and preferably located outside the processing areas.

2.1.18 Avoid having exposed overhead roof joints, pipes and ducts.

2.1.19 Electrical power supply shall be adequate to ensure the proper functioning of production equipment and laboratory instruments.

2.1.20 The condition of buildings shall be reviewed regularly, and repaired where necessary. Special care shall be exercised to ensure that building repair or maintenance operations do not adversely affect products.

2.1.21 Storage areas shall be of adequate space, provided with suitable lighting, arranged and equipped to allow dry, clean and orderly placement of stored materials and products.

2.1.21.1 Special and secured areas shall be available for storage of flammable and explosive substances, highly toxic substances, narcotics and other dangerous drugs.

2.1.21.2 Storage areas shall be laid-out to permit effective and orderly segregation of the various categories of materials stored to allow FIFO system.

2.1.21.3 Segregated storage shall be provided for rejected, recalled or returned goods.

2.1.21.4 Storage arrangements shall permit separation of different labels, as well as other printed materials to avoid mix-up.

2.1.21.5 Materials require special storage conditions such as temperature and/or humidity controls. These conditions should be monitored and records of the monitoring retained.

2.1.22 Doors that lead from production areas directly to the outside, e.g. fire exits, shall be secured against contamination.

Section 3 *EQUIPMENT*

Equipment used in the manufacturing of drug products shall be of appropriate design and construction, adequate size and suitably located in order to assure product quality and process reproducibility and to facilitate its cleaning and maintenance.

3.1 *Design and Construction*

The design and construction of equipment shall fulfill the following requirements:

3.1.1 the equipment surfaces coming in contact with any raw material, intermediate, bulk or finished product shall not be reactive, additive or

absorptive so as to alter safety, strength, identity, quality or purity of the drug beyond the established limits

3.1.2 equipment shall not adversely affect the product through leaking valves, lubricant drips, inappropriate repairs, maintenance, modifications or adaptations

3.1.3 materials required for specific operations, such as lubricants or coolants shall not come into contact with any in-process materials as to alter the strength, safety, identity, quality, or purity of raw material, intermediate, bulk or the finished product beyond the established limits

3.1.4 equipment shall be easily and conveniently cleanable

3.1.5 all equipment designated for use with flammable substances or chemicals shall be explosion proof

3.1.6 equipment employed for weighing, measuring, testing and recording shall be regularly checked for accuracy and calibrated according to an appropriate program and procedure; and records shall be maintained. Calibration conducted shall be traceable to a primary standard of calibration of an appropriate national government agency and other reliable agency. Records of calibration shall be provided and maintained

3.1.7 filters for liquid filtration used in the processing of products shall not release fibers or substances into such products.

3.2 ***Installation and Location***

3.2.1 Equipment shall be suitably installed and located to eliminate cross-contamination.

3.2.2 Equipment shall be located at a sufficient distance from other equipment to avoid congestion and to ensure that products do not become admixed or confused with one another.

3.2.3 All open mechanical belts and pulleys shall be equipped with safety guards. Water, steam and pressure or vacuum lines shall be installed so as to be easily accessible during all phases of operation. These shall be adequately labeled and marked to be easily recognized.

3.2.4 Each piece of equipment shall be clearly marked with an identifying number. This number will be used on all batch directions to designate the particular unit or apparatus used in that specific batch.

3.2.5 All pipes, tanks, jackets for steam or coolant shall be properly insulated to prevent possible injury and to minimize energy loss.

3.2.6 Piping to equipment designated for use with the pressurized steam shall be properly trapped and drained.

3.2.7 Heating, ventilation, air conditioning, potable water, purified water, distilled water, clean steam, compressed air, gases and other support systems must undergo validation.

3.3 *Maintenance*

3.3.1 Equipment shall be subjected to regular maintenance checks at appropriate intervals to prevent malfunctions or contamination that can alter the strength, safety, identity, quality, or purity of the product beyond established limits.

3.3.2 Written procedures shall be established and followed for maintenance of equipment. The preventive maintenance program shall be structured to assure:

3.3.2.1 all equipment requiring preventive maintenance is identified

3.3.2.2 the preventive maintenance schedule allocates priorities for maintenance

3.3.2.3 the frequency for preventive maintenance for each equipment is identified

3.3.2.4 the maintenance records are kept

3.3.2.5 that a preventive maintenance activity for critical pieces of equipment exceeds the scheduled time interval for that activity, quality assurance is advised of the deviation in the maintenance schedule.

3.3.3 A written record of major equipment maintenance and use shall be included in individual equipment logs which also identifies the date, time, product, strength and batch or lot number of each batch processed. For equipment used solely for one product the record can be included in the production batch records.

3.3.4 A comprehensive program shall cover equipment calibration. Records shall be maintained and to highlight trends and/or exceptional reports.

3.4 *Validation*

3.4.1 Validation shall be conducted following a Validation Protocol. Equipment validation involves three distinct stages:

3.4.1.1 Installation Qualification

3.4.1.2 Operational Qualification

3.4.1.3 Performance Qualification/Product Valida- tion (sometimes referred as process validation)

3.4.2 There are a number of basic principles related to validation of new equipment. The detail and scope of an installation and operational

qualification exercises is related to the complexity of the equipment involved and the critical nature of that equipment with respect to the quality of the final product. Nonetheless, basic principles shall be adhered to whether it is the installation and operation of a simple weighing balance or an autoclave. These basic principles are:

3.4.2.1 Install the equipment in accord with an installation plan per supplier's manual or by any special purchase requirements.

3.4.2.2 The requirements for calibration, maintenance and cleaning are developed first as draft procedures, reviewed and finally issued as authorized standard operating procedures (SOP) and become part of the SOP program of the company.

3.4.2.3 Establish operating requirements and conduct test to assure equipment is operating correctly, under normal and worst case conditions.

3.4.2.4 Finalize and document operator-training requirements pertaining to new equipment.

Section 4 *SANITATION AND HYGIENE*

High level of sanitation shall be practiced in every aspect of manufacturing drug products. The scope of the sanitation and hygiene program covers personnel, premises, equipment and apparatus, production materials and containers and anything that could become a source of contamination to the product. Potential sources of contamination shall be eliminated through an integrated comprehensive program of sanitation and hygiene. In all instances, the sanitation and the hygiene procedures should be validated and periodically assessed to ensure that the effectiveness of the operation meets the requirements.

4.1 *Personnel*

4.1.1 All personnel, prior to and during employment, shall undergo health examinations. Operators required to undertake visual inspections shall also undergo periodic eye examination.

4.1.2 Personal hygiene shall be observed by all those concerned with the manufacturing processes.

4.1.3 Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products shall not be allowed to handle raw materials, packaging materials, in-process materials, and drug products until fit to work.

4.1.4 All employees shall be instructed and encouraged to report to their immediate supervisor any health condition that may adversely affect the product.

4.1.5 Direct contact shall be avoided between the operator and raw materials, intermediate or bulk products.

4.1.6 Personnel engaged in the manufacturing of drug products shall wear clean clothing appropriate for the duties they perform. Soiled uniforms shall not be used and be stored in closed containers until properly laundered or disposed.

4.1.7 Only authorized personnel shall enter those areas of the buildings and facilities designated as limited-access areas.

4.1.8 Personnel shall be instructed to wash their hands before entering production areas. Signs to this effect shall be posted.

4.1.9 Smoking, eating, drinking, chewing and other activities; keeping plant, food, drink, smoking material and personal medicines shall be restricted to specific areas and not permitted in production, laboratory, storage areas and other areas where they might adversely affect product quality.

4.1.10 Personal hygiene procedures including requirement of using protective clothing shall apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees on company property, e.g. contractor's employees, visitors, senior management and inspectors.

4.2 ***Premises***

Premises used for manufacturing drug products shall be suitably constructed to facilitate good sanitation.

4.2.1 Adequate, well-maintained, and properly sited facilities shall be provided.

4.2.2 Suitable locker facilities shall be provided in appropriate locations.

4.2.3 The preparation, storage and consumption of food and beverages shall be restricted to cafeteria/lounge. These facilities shall meet sanitary standards.

4.2.4 Waste materials shall not be allowed to accumulate. It shall be collected in suitable receptacles for removal to collection points outside the buildings and should be disposed off properly in a safe sanitary manner at regular and adequate intervals.

4.2.5 Rodenticides, insecticides, fumigating agents and sanitizing materials used within the premises shall not be permitted to contaminate equipment, raw and packaging materials, in-process materials or finished products.

4.3 ***Equipment***

4.3.1 Equipment shall be cleaned according to established procedures immediately after use and shall be kept or stored in a clean condition

and be checked for cleanliness prior to each use to ensure that all products or materials from the previous batch has been removed.

4.3.2 Vacuum or wets cleaning methods are to be preferred. Compressed air and brushes shall be used with care and avoided if possible, as they increase the risk of product contamination.

4.3.3 Cleaning and storing of mobile equipment and storing of cleaning materials shall be done in rooms separated from processing areas.

4.3.4 Written procedures in sufficient detail shall be established and followed for cleaning and sanitizing equipment, and containers used in the manufacture of drug products. These procedures shall be designed to prevent equipment contamination by cleaning or sanitizing agents and shall include responsibility for cleaning schedule, method, equipment and materials used in cleaning operations, the method of disassembling and reassembling equipment as appropriate to assure proper cleaning and sterilization, removal of previous batch identification, protection of clean equipment from contamination prior to use.

4.3.5 Records of cleaning, sanitizing, sterilization and inspection prior to use shall be maintained.

4.3.6 Weighing and measuring equipment shall be calibrated regularly for accuracy and precision.

Section 5 *STORAGE OF STARTING AND PACKAGING MATERIALS, INTERMEDIATES, BULK PRODUCTS AND FINISHED PRODUCTS*

5.1 Materials shall be stored in an orderly manner to prevent any risk of mix-up or contamination and to facilitate inspection and maintenance. Materials shall be stored off the floor and sufficiently spaced.

5.2 The materials shall be stored under suitable environmental condition. Any special storage condition shall be provided and conditions monitored.

5.3 Outdoor storage is permissible for materials in secured containers (e.g. metal drums) and whose condition will not be adversely affected by exposure to temperature or other conditions.

5.4 Storage operations shall be adequately segregated from other operations. Storage operations shall be adequately segregated from other operations.

5.5 All deliveries to storage areas, including returns, shall be properly documented. Each batch of starting and packaging materials, intermediates, bulk products and finished products in storage areas shall have an inventory system. Inventory system shall be periodically reconciled and if there is any discrepancy found it shall be verified and justified when the quantity approved for use is different from the original receipt or delivery. This shall be documented with a written explanation.

5.6 Raw materials and packaging materials shall be returned to storage areas following clearly defined operating procedures.

5.7 All raw materials, packaging materials, intermediate and bulk products returned to storage areas shall be properly documented and reconciled.

5.7.1 All raw materials and packaging materials delivered shall be checked for proper identity, condition of container and approval of quality control unit.

5.7.2 Rejected raw materials and packaging materials shall not be stored together with approved materials. They are to be stored in the assigned location for rejects.

5.7.3 Printed packaging materials shall be stored in a restrictive storage area and dispensed under strict supervision.

5.7.4 The First Expiry First Out system (FEFO) on approved raw materials shall be used.

5.7.5 Raw materials shall be re-tested for identity, strength, quality and purity as necessary e.g. after storage periods, or after exposure to air, heat or other conditions that may adversely affect their quality.

5.7.6 There shall be a written procedure or system on re- evaluation of residual raw and packaging materials before use.

5.7.7 All incoming, outgoing and remaining materials shall be recorded. The record shall contain information on suppliers, batch or lot number, quantity and number of containers, control number, date of receipt or issuance, date of release and date of expiry if any.

5.7.8 Each batch of starting materials delivered shall have assigned reference number or control number that will identify the delivery or batch throughout storage and processing. This number shall appear on the labels of the containers and permit access to records where full details of the delivery or batch to be checked. Different batches within one delivery shall be regarded as separate batches for sampling, testing and release purposes.

5.7.9 Each starting material employed prior to release for use shall be in compliance with its material specification and be labeled with the name designated in the specification. Unauthorized abbreviations, codes or names shall not be used.

5.7.10 Each delivery shall be visually checked on receipt for general condition, integrity of container(s), spillage and possible deterioration, and be sampled by personnel and methods of sampling approved by the quality control manager. The sample shall be regarded as separate batches for sampling, testing and release purposes.

5.7.11 Steps shall be taken to provide assurance that all containers in a delivery contain the correct starting materials, and to safeguard

against mislabeling of the containers by the supplier. A listing of standard names of chemical materials shall be available for reference.

5.7.12 Deliveries of starting materials shall be held in quarantine until approved and released for use on the authority of the quality control manager or his/her designate.

5.7.13 Labels indicating status shall only be attached to starting materials by persons authorized by the quality control. Such labels shall be of a nature or form which prevents confusion with any similar labels previously used by the material supplier (e.g. they shall bear the company name or logo). As the status of the material changes, the status-labels shall be changed accordingly.

5.7.14 Stocks of starting materials shall be inspected at intervals to ensure that the containers are properly closed and labeled, and in good condition. These shall be re-sampled and re-tested and shall be initiated by the application of retest labels and/or by similarly effective documentary systems.

5.7.15 Starting materials, particularly those that may deteriorate on exposure to heat shall be stored in a strictly controlled temperature room.

5.7.16 Only an authorized person using an approved procedure shall issue starting materials. Stock record shall be maintained so that stock reconciliation can be made or equivalent.

5.7.17 Segregated dispensing areas suitably equipped to avoid cross-contamination shall be provided. Specially equipped production areas may be solely designated for the dispensing of sensitizing or highly toxic materials such as hormones, cytotoxic agents and certain antibiotics.

5.7.18 All rejected starting materials shall be conspicuously identified, placed separately under lock and key and shall be destroyed or returned to the supplier as soon as possible.

5.8 Intermediate, Bulk and Finished Products

5.8.1 Intermediates, bulk products and finished products shall be held pending quality control testing and disposition.

5.8.2 Intermediates, bulk products and finished products shall be checked to verify that the material delivered agrees with the delivery documentation.

5.8.3 Each container of intermediates, bulk products and finished products delivered to the storage area shall be checked for proper identification and condition.

5.8.4 If the identity or condition of any container of intermediates, bulk products and finished products is suspected, or does not comply with the requirements of identity or condition, that container shall be retained in the quarantine for quality control inspection and disposition.

Section 6 *PRODUCTION*

Production shall follow defined procedures capable to provide assurance of consistently yielding drug products that conform to their specifications.

6.1 *Basic manufacturing requirements:*

6.1.1 Equipment shall be technically suitable, well sited (so as not to interfere with other operations), easy to clean and maintain. The design, siting and operation of equipment shall ensure that no contamination from foreign materials such as rust, lubricants, abraded particles or foreign ingredients should occur.

6.1.2 A high standard of factory sanitation and personal hygiene is necessary to achieve the objectives of protecting each product from contamination by the environment or by the operations and protecting products from cross contamination with other products. Emphasis in this important areas shall be placed on written programs to ensure that the steps have been logically thought out and validated.

6.1.3 The manufacturer shall clearly define its system of information and control. The documentation system shall: provide unambiguous sections to be followed, provide confirmation of performance, allow calculation to be checked and to allow the accountability and traceability of operators, materials and batch disposition.

6.1.4 Manufacturing facilities and methods shall be designed to prevent cross-contamination.

6.1.5 There shall be sufficient space provided to minimize clutter and untidy work practices to assure orderly material receivals, warehousing and processing activities. The layout of rooms, corridors and areas, shall provide for logical movement of materials and personnel with minimal traffic and for operations to be carried out in defined areas.

6.2 *Process Validation*

A company should only use validated manufacturing processes. All established processes, materials or products, procedures, activities, systems, equipment or mechanism used in manufacture or control procedures may be validated utilizing a retrospective approach.

6.2.1 All production procedures shall be properly validated, validation shall be conducted in accordance with previously defined procedures and a record of the results shall be maintained. The extent and degree of validation depend on the nature and the complexity of the product and process.

6.2.2 The validation program and documentation shall provide evidence of the suitability of materials, the performance and reliability of equipment and systems and the competency of personnel.

6.2.3 When any master processing procedure is adopted, steps shall be taken to demonstrate that it is suitable for routine operation and that

the defined process, using materials and equipment specified, will consistently yield a product of the required quality.

6.2.4 Significant changes in process, equipment or materials shall be accompanied by further validation steps to ensure that the changes continue to yield consistently a product of the required quality.

6.2.5 To ensure that processes and procedures remain capable of achieving the intended results, these shall routinely undergo critical appraisal.

6.3 *Contamination*

The presence in a drug product of any contaminant is unacceptable.

The air, water, personnel and all surfaces that come in contact with the product during the manufacturing process are all potential sources of contamination. Regular monitoring of the manufacturing environments shall be instituted to assure that the risk of contamination is detected early and corrective actions are undertaken.

6.4 *Batch and Lot Numbering System*

There shall be a system describing the details of the batch and/or lot numbering set up to ensure that each batch or lot of intermediate, bulk or finished product is identified with a specific batch or lot number.

6.4.1 A batch and/or lot numbering system applied to a processing state and to the respective packaging stage shall be related to each other.

6.4.2 The batch and/or lot numbering system shall be defined to assure that the same batch or lot numbers will not be repeatedly used.

6.4.3 Batch or lot numbers allocation shall be immediately recorded in a logbook or any other means of recording. The record shall include date of allocation, product identity and size of batch or lot.

6.5 *Weighing and Dispensing*

Only approved materials shall be permitted into the dispensary area. The dispensary area is an area that permits a transition from “dirt” bulk storage containers to clean containers for the dispensed materials intended for manufacture. This stage is also the time when pallets constructed of plastic or some other cleanable and impervious materials are used for storage of dispensed materials and transport of bulk dispensed materials throughout the manufacturing areas. The dispensary is an example of a “gray” area that is a transition area from a black area (the warehouse) to a white area (the processing area/s) where the cleanliness level or the reduction of transfer of contaminants is achieved by a simple operation. Another example is operator change and wash procedures.

6.5.1 The methods for handling, weighing, counting and dispensing raw materials, packaging materials, intermediate products, and bulk products shall be included in written procedures.

6.5.2 All issuance of raw materials, packaging materials, intermediate products, and bulk products including those for additional materials for production orders already dispensed shall be properly documented.

6.5.3 Only raw materials, packaging materials, intermediate products and bulk products which are approved by quality control can be dispensed.

6.5.4 To avoid mix-up, cross-contamination, loss of identity and confusion, only the relevant raw materials, intermediate products and bulk products shall be within the dispensing areas. After weighing, dispensing and labeling, the raw materials, intermediate products and bulk products shall be transported and stored in a manner that will preserve its integrity until further processing.

6.5.5 Prior to weighing and dispensing, each container of raw materials shall be checked for proper labeling, including the approval from quality control.

6.5.6 Capacity of weighing and measuring equipment used shall be appropriate to the amount of materials to be weighed or measured.

6.5.7 For any weighing or measuring operation, two persons shall independently verify the correctness of the identity and amount of weighed or measured materials.

6.5.8 Weighing and dispensing areas shall be maintained in a clean condition.

6.5.9 Weighing and dispensing operations shall be carried out with clean equipment.

6.5.10 Dispensed raw materials, intermediate and bulk products shall be rechecked for identity and accuracy and signed by the production supervisor or equivalent prior to delivery to the production area.

Processing

6.5.11 All materials utilized in processing shall be checked for its identity and weight against the batch record before use.

The environment of an area shall be monitored and controlled to the degree required for the operation to be performed. Before any processing operation begin steps shall be taken to ensure that the work area and equipment are free from any material product or document not required for the current operation

6.5.12 All equipment employed in processing shall be checked before use. Equipment should be certified in writing as clean before use.

6.5.13 All operation shall be performed in accordance with the written procedures. Any deviation shall be justified and reported.

6.5.14 Containers and closures used for materials awaiting processing, for intermediate products and for bulk products shall be clean and of a

nature and type which prevent contamination or deterioration of the product or materials.

6.5.15 All containers and equipment holding intermediate products shall be properly labeled as to identify the material and stage of processing. Before applying the labels, all inappropriate labels or marks previously applied shall be completely removed or crossed out.

6.5.16 All intermediate and bulk products shall be properly labeled and quarantined until approved and released by quality control.

6.5.17 All in-process intermediate and bulk controls shall be accurately recorded at the time of performance. All step-wise activities in the processing operation indicated in the batch processing record shall be signed and dated at the time of completion of the activity.

6.5.18 The actual yield of each processing step of a production batch shall be recorded and checked against the theoretical yield.

6.5.19 In all stages of processing, particular attention shall be given to the possibility of cross-contamination.

6.6 *Dry Materials and Products*

6.6.1 To overcome problem of dust control and cross-contamination created in handling of dry materials and products, special attention is needed in the design, maintenance and use of premises and equipment. Enclosed dust collecting systems or other suitable methods shall be employed.

6.6.2 Effective dust extraction systems shall be installed with discharge points situated to avoid contamination of other products or processes. Effective filtration or other appropriate systems shall be installed to retain dust.

6.6.3 To protect the product against contamination with fragments of metal, glass or wood, special care shall be taken. Use of glass equipment is to be avoided. Screens, punches, sieves and dies shall be checked for wear or breakage before and after each use.

6.6.4 Care shall be taken to guard against tablets or capsule that may lodge and remain undetected in equipment, counters or bulk containers.

6.7 *Mixing and Granulation*

6.7.1 Mixing, sifting and blending equipment shall be fitted with a dust control system.

6.7.2 Critical operating parameters (e.g. time, speed and temperature) for each mixing, blending and drying operation shall be laid down in the master production document, monitored during processing and recorded in the batch records.

6.7.3 Filter bags fitted to fluid bed dryers shall be specific to one product use.

6.7.4 Solutions or suspensions shall be freshly prepared and consumed to minimize the risk of contamination or microbial growth.

6.8 *Compression*

6.8.1 Tablet compressing machines shall be provided with effective dust control facilities.

6.8.2 There shall be a suitable physical, procedural and labeling control to prevent mix-up for all in-process tablets.

6.8.3 Accurate weighing equipment shall be used for in-process monitoring of tablet weights.

6.8.4 Tablets removed from a compressing cubicle or station for testing or other purposes shall not be returned to the batch.

6.8.5 Rejected or discarded tablets shall be placed in containers properly identified and the quantity shall be recorded in the batch processing record.

6.8.6 Punches and dies shall be examined before each use for wear and tear. A record of their use shall be maintained.

6.9 *Coating*

6.9.1 Air supplied to coating pans for drying purposes shall be filtered and of suitable quality.

6.9.2 Coating solutions shall be prepared in a separate cubicle within the coating room and used immediately to prevent microbial growth. Their preparation and use shall be documented.

6.10 *Hard Capsule filling*

6.10.1 Empty capsule shells should be regarded as starting materials. They should be stored under appropriate conditions to prevent drying and brittleness or other effects of moisture.

6.11 *Liquids, Creams and Ointments*

6.11.1 Liquids, creams and ointments shall use closed system of production and transfer to protect the product from contamination.

6.11.2 Tanks, containers, pipework and pumps shall be designed and installed so that they may be readily cleaned and sanitized. In particular, equipment design should include a minimum of dead-legs or sites where residues can accumulate and promote microbial proliferation.

6.11.3 High quality stainless steel is the material of choice for parts coming into contact with product.

6.11.4 The chemical and microbiological quality of the water used shall be specified, monitored and documented. Water shall be of potable quality and have an acceptable microbial count before use.

6.11.5 Where pipelines are used for delivery of ingredients or supply of bulk products, care should be taken to ensure that such systems are easy to clean. Pipework shall be designed and installed so that it may be readily dismantled and cleaned.

6.11.6 Measuring systems shall be verified as accurate. Where dipsticks are used, they shall be used only with the particular vessel for which they have been calibrated. They shall be made of suitable non-reactive, non-absorptive material (e.g. stainless steel).

6.11.7 Care shall be taken to maintain the homogeneity of mixtures, suspensions, etc. during filling. Mixing and filling processes should be validated. Special care shall be taken at the beginning of a filling process, after stoppages and at the end of the process to ensure that homogeneity is maintained.

6.11.8 When the finished product is not immediately packaged, the maximum period of storage and the storage conditions shall be specified and adhered to.

Section 7 *PACKAGING*

The function of the packaging operation is to subdivide and control bulk product. These operations shall be performed under strict control designed to protect the identity, integrity and quality of the final package.

7.1 All packaging operations shall proceed in accordance with a SOP. Details of the operation shall be recorded on the batch packaging record.

7.2 Before a packaging operation begin, checks shall be carried out to ensure that the work area and equipment are clean and free from any products, product residues or documents not required for the operation.

7.3 Finished bulk product and packaging component shall be checked and verified for their correctness against the master packaging procedure or a specific packaging order.

7.4 *Coding of Components*

7.4.1 Labels, cartons and other components that require pre-coding with a batch number or lot number, expiration date, or other information specific to a given packaging order shall be strictly controlled at all stages of the process, from the time of delivery from the warehouse until they become parts of finished packages.

7.4.2 Components for coding shall be stored in sealed containers within an appropriate area for proper security and segregation.

7.11.1 Coding of components shall take place in an area isolated from other packaging operations. To avoid mix-up, only one particular printed packaging material is permitted in a single coding station at a time. Adequate segregation shall be maintained between coding stations.

7.4.3 All coded materials shall be checked before transfer to packaging.

7.4.4 Special emphasis shall be given to the control of pre-printed packaging materials particularly product labels. It is important that there be rigorous control from the draft text through artwork approval, printing, receipt and quality control, storage, verification, issue, application to the product unit and disposal or return of surplus. Pre-printed packaging materials shall be identified by a component code number as part of the component printed text. These code numbers shall be unique to each amendment of text. In addition to the code numbers, there shall be a system of bar codes that is also part of the printed text and is unique for each amendment.

7.4.5 All approved pre-printed packaging materials (including "approved" status labels) shall be stored separately in a locked area. Access to this area shall be restricted to authorized persons.

7.4.6 Pre-printed materials shall not be over-printed with a different name, dosage form or strength of the product. Labels shall be counted on receipt or at the time of issuance or on line. Where batch numbers and expiry date are added to labels off-line, this operation shall be done in a segregated, lockable area which maybe a label store. The coding process shall be documented and preceded with an area clearance check that follows the standard operating procedure. A known number of each label or pre-printed packaging material shall be issued in sealed containers for each packaging run.

7.5 *Line Clearance*

7.5.1 Immediately prior to the placement of materials on the packaging line, a line clearance check shall be made by a designated responsible packaging person in accordance with a written line clearance procedure to:

7.5.1.1 verify that all materials and packaged products from the previous packaging operation have been removed from the packaging line and line area

7.5.1.2 check the line and immediate area for general cleanliness and

7.5.1.3 verify that the equipment has been properly cleaned.

7.5.2 The person responsible for the line check shall initial and date the batch packaging documentation indicating completion of that check

7.5.3 All packaging and labeling materials shall be carefully checked for identity and conformity to the description in the batch documentation

7.5.4 A check shall be made of the batch number and expiry imprinted on pre-printed packaging materials at start up and regular intervals through the packaging run. The expiry date for a product should be calculated from the date of the final processing stage of the product before packaging

7.5.5 Upon completion of the packaging run unused, un-coded labels and pre-printed packaging materials shall be counted and held for destruction or be returned to the store. Damaged or defaced pre-printed packaging materials shall be counted or closely estimated.

7.5.6 A reconciliation shall be made between the issued quantities of pre-printed packaging materials and the respective numbers accounted for on product units, as samples on bulk shipper cartons and also the number destroyed or defaced.

7.6 *In-Process Control*

7.6.1 Written in-process control procedures shall be followed. These procedures shall describe the point of sampling, frequency of sampling, number of samples to be taken, specifications to be checked, and the limits of acceptability for each specification.

7.6.2 In addition, in-process control shall include, but not limited to, the following general procedures :

7.6.2.1 the product fill or count shall be checked at the start of a packaging run and

7.6.2.2 finished packages shall be checked throughout the run at regular intervals to assure that these fully comply with the specifications and that all components are those specified in the master packaging procedure.

7.6.3 Results of in-process tests/inspection shall be recorded, and these documents shall become a part of the batch packaging record.

7.7 *Operating Practices*

7.7.1 Risk of packaging errors can be minimized by the following means :

7.7.1.1 the use of roll-feed labels

7.7.1.2 on-line batch coding

7.7.1.3 use of electronic code readers and labels counters

7.7.1.4 labels and other printed materials designed with distinct marks for different products and

7.7.1.5 in addition to visual checks during the packaging run, independent quality control checks during and at the end of the run should be performed.

7.7.2 Products of similar appearance shall not be packaged in close proximity unless there is physical segregation.

7.7.3 At each packaging line the name and batch of the product being packaged shall be displayed.

7.7.4 Containers in which bulk product, partly packed product, or sub-batch is stored shall be labeled or marked with an indication of product identity, quantity, batch and status.

7.7.5 Containers to be filled shall be supplied to the packaging line or station in a clean condition.

7.7.6 All packaging personnel shall be trained to recognize in process control requirements and report any deviation they may detect while performing their specific responsibilities.

7.7.7 Packaging areas shall be cleaned at frequent intervals throughout the workday and at any time a spill of material occurs. Personnel engaged in cleaning shall be trained to avoid practices that could cause mix-up or cross-contamination.

7.7.8 Any printed packaging material found during clean up operation shall be turned over to a supervisor, and be placed in a designated container for reconciliation and destroyed at the end of a packaging run.

7.7.9 Products filled into their final containers while waiting for labeling shall be segregated and marked so as to avoid mix-up. This practice should be avoided and only be instituted in exceptional circumstances.

7.7.10 Packaging equipment whose parts do not normally come in contact with the bulk product but in which dust, debris, packaging components or product might collect and later fall into the product or otherwise become a contaminant or source of mix-up, shall be appropriately cleaned.

7.7.11 Measures shall be taken to control the spread of dust during packaging especially of dry products. Segregated packaging areas are necessary for some products e.g. potent low dose or toxic products and sensitizing agents. Compressed air shall never be used to clean equipment within an operation packaging area where there is danger of cross-contamination.

7.7.12 Brushes shall be restricted in use because of the contamination hazard of hairs or bristles and/or particles held in the brushes.

7.7.13 Personnel shall place packaging components or products in appropriate properly identified containers.

7.7.14 Essential supplies, such as lubricants, adhesive, inks, cleaning fluids, etc. shall be kept in containers that look completely different from any container that is used for product packaging and shall be clearly labeled as to their contents.

7.8 *Completion of the Packaging Operation*

7.8.1 On the completion of the packaging operation, the last production package shall be carefully checked to confirm that it fully agrees with the master packaging procedure.

7.8.2 Only finished goods from a single packaging operation shall be placed on a pallet. Any partial carton and the quantity contained shall be indicated on the carton. The removal of excess packaging components and bulk product, after reconciliation, shall be closely supervised to ensure that only the packaging components and bulk product permitted to be returned to the warehouse are saved and that these are properly identified.

7.8.3 A responsible person shall oversee the counting and destruction of non-returnable packaging components and bulk product. All unused coded materials shall be reconciled and destroyed. Quantities destroyed shall be recorded on the batch packaging record.

7.8.4 A responsible person shall calculate and record the net used for all packaging components and bulk product.

7.8.5 Any unexplained yield discrepancies or failure to comply with the specifications shall be thoroughly investigated, with consideration extended to other batches or other products which might also be affected.

7.8.6 After acceptable reconciliation, the finished product shall be delivered to the quarantine finished product area pending final release by the quality control department.

Section 8 *FINISHED PRODUCT QUARANTINE AND DELIVERY TO WAREHOUSE*

Finished product quarantine is the last point of control before the product enters the warehouse and becomes available for distribution to the market. Strict controls shall be exercised to ensure that the product and its packaging records meet all specified requirements before release to the warehouse.

Written procedures shall describe the transfer of finished product into the quarantined area, storage while waiting approval, requirements that shall be met for approval and subsequent transfer to the finished goods warehouse.

Pending release by the quality control unit, the entire packaged batch or lot shall be held in the finished goods quarantine.

No material except samples for the quality control unit shall be dispensed from any product lot or batch while it is being held in the finished goods quarantine area.

Physical access to the products under quarantine shall be restricted, and only those persons actually required working in the area or who have been properly authorized to enter the area should be allowed access.

Any finished product that requires special storage conditions shall be appropriately labeled to show the required storage conditions, and the material shall be stored in quarantine under the specified conditions.

Final quality control release of the product shall be preceded by the satisfactory completion of the following events :

8.6.1 finished products meet quality control requirements for all processing and packaging specifications

8.6.2 retention by quality control of sufficient finished market containers as retained samples for future testing; packaging and labeling meet all require- ments as checked by quality control

8.6.3 the reconciliation of printed packaging components is acceptable and

8.6.4 marketed packages received in the finished goods quarantine area are reconciled with the amount shown on the transfer documents.

8.7 After the quality control unit has approved a batch or a lot, the material shall be removed from the finished goods quarantine area to the finished goods storage. If required by BFAD, antibiotic products should not be released without BFAD certification.

8.8 Upon receipt of the finished goods, the warehouse unit shall make entry in the corresponding inventory card or other system for the batch received.

8.9 ***Control record for shipment of finished products***

8.9.1 A system designed to control the shipment of finished products shall assure that the first expiry material is distributed first.

8.9.2 The system shall generate records from which the distribution of each batch or lot of drug product can be readily determined to facilitate investigation or recall if necessary.

8.9.3 Written procedures describing the distribution of products (drug, devices and other products) shall be established and followed.

Section 9 *QUALITY CONTROL*

Quality Control is an essential part of Good Manufacturing Practices to provide assurance that the products will be consistently of a quality appropriate to their intended use. The involvement and commitment of all concerned at all stages are mandatory towards the achievement of this quality objective from the start of manufacturing to the distribution of the finished product. An independent quality control unit shall be established.

9.1 *General Provisions*

9.1.1 A quality control system shall be developed and designed so as to ensure that finished products contain the correct materials of specified quality and quantity and are manufactured under proper conditions following standard procedures, thereby they will consistently meet the established specifications for identity, strength, purity, quality and safety.

9.1.2 Quality control involves all analytical functions conducted in the laboratory, including sampling, inspecting and testing of starting materials, intermediate, bulk and finished products. It also includes stability test, environmental monitoring program, validation tests, review of batch documentation, sample retention program and establishing and maintaining current specification of materials, products and their test methods.

9.1.3 Documentation and release procedures applied by the quality control unit shall ensure that the necessary tests are carried out, and that the materials are not released for use, nor products released for distribution and sale until their quality has been determined to meet specifications.

9.1.4 The quality control unit shall have the following principal duties:

9.1.4.1 to establish and revise control procedures and specification

9.1.4.2 to prepare detailed written instructions for carrying out each inspection, test and analysis

9.1.4.3 to establish written sampling plans and sampling procedures

9.1.4.4 to maintain retained sample for future reference

9.1.4.5 to release or reject each batch of starting material, intermediate, bulk or finished product

9.1.4.6 to review all documentation relating to the batch processing, packaging and testing of each batch of finished product before authorizing release for distribution

9.1.4.7 to evaluate the stability of all finished products on an on-going basis and raw materials where necessary, and to establish instructions for the storage of materials and products within the manufacturing plant on the basis of their stability data

9.1.4.8 to establish expiration dates and shelf-life of raw materials and finished products based on their stability data and storage condition

9.1.4.9 to evaluate and approve any reprocessing procedure for products

9.1.4.10 to accredit those approved suppliers of raw and packaging materials capable of and reliable for supplying starting materials that meet the company's established quality specifications

9.1.4.11 to take part or assist in validation program

9.1.4.12 to evaluate all complaints received or deficiencies noted about any batch, if necessary in co-operation with other units of the company, and to take appropriate corrective action

9.1.4.13 to prepare secondary reference standards as specified in the current procedure for testing and to store these standards under proper conditions

9.1.4.14 to maintain analytical records of the tests of all samples taken

9.1.4.15 to evaluate returned drug products and determine whether such products could be released or reprocessed or shall be destroyed

9.1.4.16 to participate in the self-inspection program with other units of the company and

9.1.4.17 to recommend toll manufacturing operations after evaluating the toll manufacturer's capability to produce products that meet the company's specified quality standards.

9.2 ***Control Laboratory***

9.2.1 ***Premises***

9.2.1.1 Control laboratories shall be designed, equipped and of sufficient space to suit relevant operations.

9.2.1.2 Provisions shall be made for the proper and safe storage of waste materials awaiting disposal. Toxic substance and inflammable materials shall be stored in suitably designed and storage.

9.2.1.3 The laboratories shall be physically separated from the production rooms. Biological, microbiological and chemical laboratories shall be segregated from each other. Air handling facilities for biologicals and microbiologicals should be separate from process air handling facilities.

9.2.1.4 A separate room shall be provided for instruments to protect these against electrical interference, vibration, contact with excessive moisture and other external factors or where there is need to isolate the instrument.

9.2.1.5 The design of the laboratory shall take into account the suitability of construction materials, fume prevention and ventilation. Separate air handling units shall be installed for biological, microbiological and radioisotope laboratories.

9.2.1.6 All service pipings/pipelines and devices shall be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.

9.2.1.7 A safety shower and eye-bath shall be provided in close proximity to the laboratory working area.

9.2.2 ***Personnel***

9.2.2.1 Each individual engaged in the supervision or conduct of a laboratory operation shall have proper education, training and experience or combination thereof, to enable the individual to perform the assigned functions. Their duties and responsibilities shall be clearly defined in job descriptions or by other suitable means.

9.2.2.2 Personnel shall wear protective clothing and safety equipment such as respirators or face masks, safety glasses and acid or alkali resistant gloves appropriate to the duties being performed.

9.2.3 ***Equipment***

9.2.3.1 Control laboratory equipment and instruments shall be suitable to the testing procedures undertaken.

9.2.3.2 Standard operating procedures shall be available for each instrument and equipment

9.2.3.3 Equipment and instrument shall be serviced and calibrated at pre-specified intervals and their records shall be maintained. Pre-check of the instrument to ensure its satisfactory functioning shall be conducted daily or prior to using the instrument for performing an analytical test.

9.2.3.4 The date of calibration, servicing and due date of the next calibration shall be clearly displayed on the equipment or by other appropriate means. Provisions shall be made to indicate failure of equipment or services to equipment. Defective equipment shall be withdrawn from use until the defect has been rectified.

9.2.4 **Reagents and Culture Media**

9.2.4.1 All reagents and culture media shall be recorded upon receipt or preparation.

9.2.4.2 Reagents made up in the laboratory shall be prepared following written procedures and appropriately labeled. The label shall indicate the concentration, standardization factor, shelf-life, re-standardization due date and storage conditions. The label shall be signed and dated by the person preparing the reagent.

9.2.4.3 Both positive and negative controls shall be applied to verify the suitability of culture media. The size of the inoculum used in positive controls shall be appropriate to the sensitivity required.

9.2.5 **Reference Standards**

9.2.5.1 Reference standards shall be under the responsibility of a designated person.

9.2.5.2 Official reference standards shall be used only for the purpose described in the appropriate monograph. Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to correct deviations and to assure the accuracy of the result.

9.2.5.3 All reference standards shall be stored and used in a manner which will not adversely affect their quality. The label of reference standards shall indicate the concentration, date of manufacture, expiration date, date the closure is first opened and storage conditions where appropriate.

9.2.6 **Specifications and Testing Procedures**

9.2.6.1 Testing procedures shall be validated in the context of available facilities and equipment before they are adopted for routine testing.

9.2.6.2 Specifications and testing procedures established for each raw material, intermediate, bulk and finished product shall include specifications and testing procedures for identity, purity, quality and strength.

9.2.6.3 Testing procedures shall include:

9.2.6.3.1 amount of sample necessary for testing and retention for future analysis

9.2.6.3.2 amount of each reagent, buffer solution, etc., necessary for the tests

9.2.6.3.3 equations for computation and

9.2.6.3.4 target value and tolerance allowable for each test

9.2.6.4 Testing procedures shall include frequency for re-assaying each raw material determined by considering its stability.

9.2.6.5 All tests shall follow the instructions given in the relevant test procedure for each material or product. The result, especially where calculations are involved, shall be checked by the supervisor before the material or product is released or rejected.

9.2.6.6 A procedure should be available to describe the action taken when an out of specification result is obtained.

9.2.7 **Records of Analysis**

Records of analysis shall include :

9.2.7.1 name and batch number of sample

9.2.7.2 name of the individual who takes the sample

9.2.7.3 methods of analysis

9.2.7.4 all data, such as weight, buret readings, volumes and dilutions made

9.2.7.5 calculation in units of measurement and the formula of calculation

9.2.7.6 statement of permitted tolerance

9.2.7.7 statement of compliance or non-compliance with specification

9.2.7.8 date and signature of the person performing the test and the person verifying the calculations

9.2.7.9 statement of approval or rejection and recommendation for its disposal, signed and dated by the authorized person

9.2.7.10 the name of supplier, total quantity and the number of containers of material received and

9.2.7.11 total quantity and number of containers of raw material, packaging material, intermediate, bulk or finished product of each batch analyzed.

9.2.8 **Retention Samples**

9.2.8.1 An appropriately identified retained sample representative of each batch in each delivery of active raw material shall be retained for a specified period.

9.2.8.2 An appropriately identified retained sample representative of each batch of finished product in its complete packaging form shall be retained for a specified period. These finished product samples shall be stored under conditions that simulate market conditions as indicated on the labels.

9.2.8.3 Retained samples shall consist of at least double the quantity necessary to perform all the required tests, except those for sterility.

9.3 ***Validation***

The quality control unit shall conduct the following validation:

9.3.1 ***Validation of Assay Procedures***

The assay principle should be suitable for the prescribed application. The validation of the analytical method is intended to establish that performance characteristics such as accuracy, precision linearity of response are satisfactory. When the assay performance characteristics are not satisfactory, it will be necessary to subject the assay procedure to appropriate review, design study, revision or replacement.

9.3.2 ***Calibration of Instruments***

Calibration of the instruments specified in the testing procedure shall be conducted on a regular basis to ensure that they are always performing satisfactorily.

9.3.3 The quality control unit shall provide assistance or take part in the periodic validation tests carried out by other units, especially the production unit to ensure that each manufactured product consistently meets the established specifications.

9.4 ***Control of Starting Materials, Intermediate, Bulk and Finished Products***

9.4.1 ***Specifications***

Each specification shall be approved and maintained by the quality control unit. Periodic revisions of the specifications are necessary to comply with the latest edition of the national pharmacopoeia or other official compendia.

9.4.2 ***Sampling***

Sampling is an important operation in which only a small fraction of a batch is taken. Valid conclusions on the whole cannot be based on tests which have been carried out on non-representative samples. Correct sampling is thus an essential part of a system of quality assurance.

9.4.2.1 Personnel who take samples shall receive initial and on-going regular training in the disciplines relevant to correct sampling. This training shall include:

9.4.2.1.1 sampling plans

9.4.2.1.2 written sampling procedures

9.4.2.1.3 the techniques and equipment for sampling

9.4.2.1.4 the risks of cross-contamination

9.4.2.1.5 the precautions to be taken with regard to unstable and/or sterile substances

9.4.2.1.6 the importance of considering the visual appearance of materials, containers and labels and

9.4.2.1.7 the importance of recording any unexpected or unusual circumstances

9.4.2.2 Samples shall be representative of the batches of material from which they are taken in accordance with the approved written procedures.

9.4.2.3 The identity of a complete batch of raw materials can normally only be ensured if individual samples are taken from all the containers and an identity test performed on each sample.

9.4.2.4 The quality of a batch of raw materials may be assessed by taking and testing a representative sample. The samples taken for identity testing could be used for this purpose. The number of samples taken for the preparation of a representative sample should be determined statistically and specified in a sampling plan. The number of individual samples which may be blended to form a composite sample should also be defined, taking into account the nature of the material, knowledge of the supplier, and the homogeneity of the composite sample.

9.4.2.5 The sampling plan for packaging materials shall take account of a least the following: the quantity received, the quality required, the nature of the material (e.g. primary packaging materials and/or printed packaging

materials), the production methods, and what is known of the quality assurance system of the packaging materials applied by the manufacturer based on audits. The number of samples taken shall be determined statistically and specified in a sampling plan.

9.4.2.6 Sampling shall be carried out so as to avoid contamination or other adverse effects on quality. Containers from which sample has been taken shall be marked to show that sample has been removed from them. Sampling instructions shall include:

9.4.2.6.1 the method of sampling and the sampling plan

9.4.2.6.2 the equipment to be used

9.4.2.6.3 the amount of sample to be taken

9.4.2.6.4 instructions for any required sub-division of the sample

9.4.2.6.5 the type of sample container to be used i.e. whether it is for aseptic sampling or for normal sampling

9.4.2.6.6 any special precautions to be observed, especially in regard to sampling of sterile or noxious materials

9.4.2.6.7 the storage conditions and

9.4.2.6.8 instructions for the cleaning and storage of sampling equipment

9.4.2.7 Each sample container shall bear a label indicating:

9.4.2.7.1 name of sampled material

9.4.2.7.2 the batch or lot number reference

9.4.2.7.3 the number of container from which the sample has been taken

9.4.2.7.4 signature of the person who takes the sample and

9.4.2.7.5 the date of sampling

9.4.2.8 Sampling equipment shall be cleaned, if necessary sterilized, before and after each used and stored separately from other laboratory equipment

9.4.2.9 Care shall be taken during sampling to guard against contamination or mix-up of, or by, the material being sampled. All sampling equipment which comes in contact with the material shall be cleaned. Some particularly hazardous or potent materials may require special precautions.

9.4.2.10 Sampling plans for starting materials shall:

9.4.2.10.1 differentiate between accredited, approved and other suppliers, including new suppliers

9.4.2.10.2 differentiate between starting materials that do not bear a manufacturer's batch number and those that do

9.4.2.10.3 differentiate between materials that maybe expected to vary from container to container (for example by segregation or moisture uptake) and those that may not

9.4.2.10.4 prescribe the action to be taken where a delivery from an accredited or approved supplier has failed

9.4.2.10.5 prescribe an increased sampling rate for damaged containers or where lots do not appear to be homogenous

9.4.2.10.6 specify the extent of pooling of samples destined for chemical tests

9.4.2.10.7 require the sampling operator to initially examine each sample for evidence of deterioration, lack of homogeneity or other visible defects

9.4.2.11 Sampling plans for in-process materials shall:

9.4.2.11.1 assure a representative sample of the batch is taken for in-process tests

9.4.2.11.2 prescribe an increased sampling rate where in-process materials do not appear to be homogenous

9.4.2.11.3 specify the extent of pooling of samples destined for chemical tests

9.4.2.11.4 require sampling operator to initially examine each sample for evidence of lack of homogeneity or other visible defects

9.4.3 *Test Requirements*

9.4.3.1 *Raw Materials*

Each raw material shall be tested for conformity with specification for identity, strength, purity and other quality parameters.

9.4.3.2 *Packaging Materials*

Packaging materials shall conform to specifications, with emphasis placed on the compatibility of the material with the drug product it contains. The critical and major physical defects as well as the correctness of identity markings that may prejudice the quality of the product shall be examined.

9.4.3.3 **Intermediate and Bulk Products**

9.4.3.3.1 To ensure batch uniformity and integrity, in-process control shall be conducted by testing representative samples of intermediate and bulk product of each batch for identity, strength, purity and quality as appropriate.

9.4.3.3.2 Written procedures describing sample taking, the controls and tests or examinations to be conducted on in-process product of each batch shall be established and followed. In-process controls are intended to monitor the product yields and validate the performance of the production processes that may be responsible for causing variability in the characteristics of in-process products.

9.4.3.3.3 In-process specifications shall be consistent with the finished product specifica- tions. They shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical methods where appropriate.

9.4.3.3.4 Rejected intermediate and bulk products shall be identified and controlled under a quarantine system designed to prevent their use in further processing unless such product is

determined acceptable for reprocessing later on.

9.4.3.3.5 Quality control approval of the product is mandatory after completion of critical steps of production or after the product has been stored for a long period.

9.4.3.4 **Finished Products**

9.4.3.4.1 For each batch of finished product (drugs, devices and other products), there shall be appropriate laboratory determination of satisfactory conformance to its finished product specifications prior to release.

9.4.3.4.2 Finished products failing to meet the established specifications and any other relevant quality criteria shall be rejected. Reprocessing may be performed if feasible but the reprocessed product shall meet all specifications and other quality criteria prior to its acceptance and release.

9.4.4 Re-testing of approved materials, intermediate, bulk and finished products.

9.4.4.1 There shall be an appropriate time limit for storage of each starting material, intermediate, bulk and finished product. After this period the material or product shall be re-tested by the quality control unit for identity, strength, purity and quality. Based on the results the materials/products are either re-approved for use or rejected.

9.4.4.2 If a material is subject to unusual storage condition, it shall be re-tested and approved for use by the quality control unit prior to processing.

9.5 ***Environmental Control***

9.5.1 There shall be written procedures for environmental monitoring, for gowning, cleaning and disinfection within manufacturing areas. These procedures shall contain “target”, “alert” and “action” limits for environmental contaminants. The procedure shall include the action/s to be taken in the event that the limit is exceeded or particular indicator organisms are isolated.

9.5.2 Regular monitoring of the process water, including at the point of use, for chemical and microbiological quality. The sample size and test method employed shall be capable of detecting the presence of low levels of indicator organisms, e.g. Pseudomonas.

9.5.3 Periodic microbiological monitoring of the production environment. There are varieties of sampling techniques that are available for monitoring of microbial contamination. Each technique has its own value and is necessary to use a combination of techniques utilizing a formal sampling program to identify trends or highlight exceptional results within the manufacturing environment. These techniques are:

9.5.3.1 Air sampling

9.5.3.2 Settle plates

9.5.3.3 Particle counting

9.5.3.4 Contact plates

9.5.3.5 Hand plates

9.5.3.6 Water sampling

9.5.4 Periodic testing of the environment around the production areas for the presence of other drug product that will contaminate the product being processed.

9.5.5 Control of airborne contaminants.

9.6 ***In-Process Control***

In-process quality control tests that maybe performed for the following (where appropriate) by suitably trained process operators are:

9.6.1 ***Tablet granulation manufacture***

9.6.1.1 moisture test

9.6.1.2 sieve (screen) analysis

9.6.2 ***Compression or encapsulation process***

9.6.2.1 individual weight determination

9.6.2.2 average unit weight determination

9.6.2.3 disintegration test

9.6.2.4 friability test (compressed tablets only)

9.6.2.5 hardness test (compressed tablets only)

9.6.2.6 maintenance of x & r charts

9.6.2.7 thickness (compressed tablets only)

9.6.3 ***Tablet coating***

9.6.3.1 average unit weight

9.6.3.2 individual weight

9.6.3.3 color and coating finish

9.6.4 ***Liquid processing***

9.6.4.1 clarity at final filtration

9.6.4.2 pH

9.6.4.3 specific gravity

9.6.4.4 final batch volume

9.6.5 ***Creams, ointments, semi-solids, liniments***

9.6.5.1 active material dispersion/solubilization

9.6.5.2 pH (excluding ointments)

9.6.5.3 viscosity

9.6.6 ***Filling/Packaging Operations***

9.6.6.1 encoded batch number and expiry date

9.6.6.2 count or measures in finished pack

9.6.6.3 label appearance and adhesion

9.6.6.4 bulk material identification

9.6.6.5 cap torque

9.6.6.6 seal integrity of strip or blister pack

9.6.6.7 correctness of first and last packages

9.7 ***Packaging Control***

9.7.1 The quality control unit shall verify line clearance before the packaging operation may proceed.

9.7.2 During the packaging run the in-process control inspector will collect samples of packed unit at the beginning, middle and end of operation.

9.7.3 Packed finished products shall be quarantined until released by the quality control unit.

9.8 *Reprocessing*

9.8.1 Reprocessing shall not be performed without prior review and approval of the quality control unit.

9.8.2 The reprocessing of a batch of product shall be considered only after the potential risks have been formally evaluated and complied with specifications.

9.8.3 The methods of reprocessing shall be specifically authorized and fully documented. Documentation shall accurately record the reworking processes carried out.

9.8.4 Additional testing of any finished product that has been reprocessed and added shall be performed as required.

9.8.5 Follow-up stability study of the reprocessed product shall be conducted as necessary.

9.8.6 *Recovered Material*

9.8.6.1 Recovered material may be reprocessed by an appropriate and authorized method, provided that the material was analyzed to be suitable for such reprocessing.

9.8.6.2 The resultant product should meet its specification and product quality.

9.8.6.3 Documentation should accurately record the reworking processes carried out.

9.8.7 **Product Residues**

9.8.7.1 Residues that are not suitable for reprocessing which do not meet specifications shall not be used in subsequent batches.

9.8.7.2 The treatment of product residues and reprocessed material and the means of their inclusion in a subsequent batch shall be specifically authorized and documented.

9.8.7.3 Limits, approved by the quality control, shall be established for the amount of any such material that may be added to a subsequent batch.

9.8.7.4 Batches incorporating residues shall not be released until the batches from which the residues originated have been evaluated and found suitable for use.

9.8.8 ***Returned Goods***

9.8.8.1 A finished product returned from the manufacturer's own stores or warehouse (because, for example, of soiled or damaged labels or outer packaging) may be relabeled or incorporated in subsequent batches, provided that there is no risk to product quality and the operation is specifically authorized and documented. If such products are re-labeled, extra care is necessary to avoid mix-up or mislabeling.

9.8.8.2 Finished products returned from the market and which have left the control of the manufacturer shall be considered for re-sale, re-labeling or incorporation in a subsequent batch only after the person responsible for quality control has critically assessed them. The nature of the product, any special storage condition required, its condition and history, and the time elapsed since it was issued shall all be taken into account in this assessment.

9.8.8.3 Where any doubt arises over the quality of the product, it shall not be considered suitable for re-issue for re-use.

9.9 ***Quality Control Evaluation on Production Procedures***

9.9.1 The quality control unit shall participate in the development of the master processing procedure and master packaging procedure for each batch size of a drug product to assure uniformity from batch to batch manufactured. Any changes and adjustments in the master processing procedure or master packaging procedure shall have quality control approval prior to execution in production.

9.9.2 The quality control unit shall approve the production equipment cleaning and sanitation procedures.

9.9.3 All production and control records shall be reviewed and approved by the quality control unit to determine the manufacturing compliance with the established procedures before a batch of finished product is released for distribution.

9.9.4 Any discrepancy or failure of a batch to meet its specifications shall be thoroughly investigated. The investigation shall extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusion and follow-up action.

9.10 ***Stability Study***

9.10.1 A stability-testing program shall be designed to assess the stability characteristics of drug products and to determine storage conditions and expiration date.

9.10.2 The written program shall be followed and shall include:

9.10.2.1 sample size test intervals based on statistical criteria for each attribute examined to assure estimate of stability

9.10.2.2 storage conditions

9.10.2.3 reliable, meaningful and specific test method

9.10.2.4 testing of the product in the same packaging form as that in which the product is marketed and

9.10.2.5 testing of the product for reconstitution before and after it has been reconstituted

9.10.3 A stability study shall be performed under the following situations:

9.10.3.1 new products (usually performed on pilot batches)

9.10.3.2 new packages i.e. those differing from the prescribed standard

9.10.3.3 change in formula, processing method or source of raw materials

9.10.3.4 batches released by exception e.g. batches with properties differing from standard or reworked batches and

9.10.3.5 marketed products to confirm assigned shelf life

9.10.4 The stability data for each product unit sales pack shall be available. The prediction of the shelf life assigned to a product pack may be based on accelerated stability studies at elevated temperatures and extreme conditions. These predictions of the length of shelf-life shall at all times be conservative. Additionally, the predicted shelf-life (from accelerated studies) shall be confirmed with actual shelf-life studies of samples held at the storage (labeled) temperature.

9.10.5 The test data used to evaluate a product's shelf-life (product stability) shall be based on the results derived from the use of special analytical methods that are stability indicating.

9.10.6 The stability profile for the products shall be verified at appropriate intervals by supplementary testing of further batches of product. Where applicable, the program shall include dissolution, microbiological and preservative efficacy testing.

9.10.7 Records of stability data for all products shall be maintained in a systematic tabular or equivalent format. The collected data shall be reviewed at appropriated intervals. The assessments leading to the

determination or amendment of shelf-life and / or storage conditions shall be documented.

9.10.8 The product shelf-life program shall be documented identifying the frequency of testing, special conditions required for each study if applicable, the test procedure and the number of batches.

9.10.9 Analytical methods used for testing of samples used to determine the stability (shelf-life) of drug products should be specially designed to be a "stability indicating". These methods shall by nature of their design quantify the particular drug entity and any breakdown products. The use of chromatographic methods is particularly applicable in this area of testing.

9.10.10 If the stability data available for a product indicates that there maybe a change from acceptance specifications on storage (within the expiry date period), the specifications which each batch of that product must meet before it is released for distribution (the release specifications) shall have different or narrower ranges of acceptance requirements for the variable attributes than those to which the product must conform at anytime during its shelf-life (the expiry specifications, or compendial monograph specifications).

9.10.11 Where this distinction is made, all relevant documents shall clearly nominate "release" and "expiry" specifications respectively. Expiry specifications shall be consistent with any data accepted by the regulatory agency (BFAD) in connection with product registration and with any compendial standards applicable to the product.

9.11 ***Starting Material Supplier's Rating***

9.11.1 The quality control unit shall have joint responsibility with other relevant departments for approving vendors who have the capability and reliability to supply starting materials that meet established specifications.

9.11.2 All prospective material suppliers shall be evaluated before orders are placed. Inspections are required where possible unless the supplier's history, reputation or warranty negates the need for such inspection.

9.11.3 Inspection shall be made jointly by representatives from quality control, production and purchasing units to determine the supplier's suitability. As a prospective buyer, the representatives from the quality control, production and purchasing units shall assess the technical qualifications of the supplier and it's attitude towards quality.

9.11.4 All established material suppliers should be evaluated regularly.

9.11.5 A list of approved suppliers of starting materials shall be established and reviewed as necessary.

9.12 ***Release for supply***

9.12.1 Release for supply of finished product shall require the examination and certification by Quality Control Unit or Quality Assurance that handles and reviews the consolidated records of processing, packaging and quality control. This is to ensure compliance with all procedures, acceptable yields and reconciliation and compliance with product release specifications. The checks conducted at final release shall satisfy the following criteria:

9.12.2 Checks that all documentation and records are complete and free of obvious errors, discrepancies and anomalies

9.12.3 A check that the yield at all critical stages in the manufacture are satisfactory and comply with pre-determined quality assurance alert limits for the product manufacture

9.12.4 A check that the accountability of pre-printed packaging materials is satisfactory and the reconciliation between issued quantities and used, destroyed and returned quantities is satisfactory and that any discrepancy in the reconciliation is within a pre-determined quality assurance alert limit

9.12.5 A check that the product meets its finished product release specification

9.12.6 For a sterile product a checks should be made that the sterilization parameters for the manufacturing activities for the batch are in accord with validation requirements for the processes

The above checks may appear as a pro-forma checklist on batch documentation with a record of their review and certification by quality assurance or quality control before release. Quality Assurance is sometimes viewed as an overall management and the allocation of duties between Quality Assurance and Quality Control may vary considerably between manufacturers because of their diversity both in type and size. This is acceptable provided that all the functions are specified and carried out.

9.13 ***Product Complaints***

9.13.1 A system for handling product complaints shall be designed which includes written procedures and indicates the responsible persons through whom the complaints are to be channeled.

9.13.2 All written and oral complaints regarding a drug product shall be thoroughly investigated. The quality control unit in conjunction with the production or marketing unit shall investigate the cause of the complaints and take appropriate measures to prevent their recurrence.

9.13.3 Records of complaints and their handling shall be made and include the following information:

9.13.3.1 Contents of Complaints. It shall include:

9.13.3.1.1 name, dosage form, package form and batch number

9.13.3.1.2 date, place of occurrence, name and address of complainant and

9.13.3.1.3 nature of complaints in detail

9.13.3.2 Result of Investigation. It shall cover the following:

9.13.3.2.1 the product under complaint (its market place, the distribution condition, the condition of how the product is used, etc.)

9.13.3.2.2 the retain sample, where necessary and

9.13.3.2.3 analysis and testing records, production and storage condition records of the product

9.13.3.3 evaluation of the Results of Investigation

9.13.3.4 follow-up measures such as remedial action for improvement, reply to the complainant, or product recall

9.13.4 The product complaint records shall be maintained for a specified period.

9.14 ***Returned Goods***

The quality control unit shall be responsible for examining products that are returned because of complaints, damage, expiration or other circumstances that may prejudice the quality of the products.

9.14.1 Returned drug products shall be identified as such and stored in a separate secured area.

9.14.2 All returned products shall be critically evaluated for necessary analysis and testing in addition to physical inspection when condition warrants. Those products that meet the appropriate specifications and characteristics may be transferred to a status of finished products and returned to inventory for resale.

9.14.3 In case the returned product is redressed for resale, it shall be recoded accordingly.

9.14.4 Any returned product which is suspected of being subjected to improper storage conditions including extremes in temperature, humidity, fumes, pressure or fire shall be destroyed.

9.14.5 Returned products to be destroyed shall be handled in such a way so as to assure destruction and also prevent the possibility of the products getting into hands of unauthorized persons.

9.14.6 Records of returned products shall be maintained and shall include the name, strength, dosage form, package form, batch number, reason for the return, quantity returned, date of disposition and method of ultimate disposition.

Section 10 *DOCUMENTATION*

Documentation in any manufacturing is a part of management information system, which includes specifications, procedures, methods and instructions, reports and records and other documents that are required for planning, organizing, controlling and evaluating the whole activities of drug manufacturing.

Documentation is essential for ensuring that each personnel receives clear and detailed description of the relevant job assignment to minimize the risk of misinterpretation and error, which are normally associated with habits of communication by oral practice only.

A documentation system shall be designed such that a complete history of each manufactured batch or lot of product can be traced back to enable investigation of the batch or lot whenever it becomes necessary.

A documentation system is also required for monitoring and controlling the condition of environment, equipment and personnel.

10.1 *General Provisions*

10.1.1 Documents shall be prepared and designed carefully for easy, correct and effective use.

10.1.2 Documents shall contain records of activities within production, quality control, equipment maintenance, warehouse, distribution and other specific activities related to Good Manufacturing Practice.

10.1.3 Each document shall have the following information:

10.1.3.1 The user's company or trading name

10.1.3.2 The purpose of the document and title

10.1.3.3 A document identity number which uniquely identifies the document and indicates revision status

10.1.3.4 Date of effectivity and review, particularly in the case of Standard Operating Procedures (SOP's)

10.1.3.5 The distribution list and where copies are distributed

10.1.3.6 Page number including the total number of pages

10.1.3.7 Signature of the persons, who prepared, checked and authorized the document for use and the respective dates for these actions. In appropriate circumstances, the person who prepared the document may also carryout the requirements for the person who checks the document. Master batch documents, standard operating procedures, specifications and other documents related to/ product quality shall be authorized by the person responsible for the quality assurance or that person's delegate as well as by a production or relevant manager.

10.1.4 It shall be apparent from the document the way in which it shall be used and by whom. The reason for revision and up-to-date details shall be documented.

10.1.5 Documents shall contain all-important data, which shall be reviewed, updated or amended as necessary and formally authorized. It shall include provision for periodic review and revision.

10.1.6 There shall be a system for preventing the use of superseded documents.

10.1.7 Where documents while in use require entry of data or additional information, then the format shall:

10.1.7.1 Provide sufficient space for the entry or additional information

10.1.7.2 Allow adequate spacing between entries

10.1.7.3 Clearly indicate what is to be included

10.1.7.4 Entries or additional information shall be handwritten clearly and legibly in permanent ink.

10.1.8 Any error made or detected on a document shall be corrected in such a manner that the original entry is not lost. The correction is made close to the original entry, initialed and dated.

10.1.9 Any document containing instructions shall be clear and precise in a language easily understood by the user.

10.1.10 Each manufacturing document shall be dated, signed and authorized by the production manager and quality control manager. Departments or other persons receiving copies of the document should be listed at least on the original copy.

10.1.11 Documents shall be readily available to all parties concerned. Signature specimen of personnel involved in the manufacturing plant shall also be maintained.

10.1.12 Batch related documents and records as well as reference sample of finished drug product and starting material shall be retained for a

period specified by the manufacturer or the relevant government authority.

10.2 *Specifications*

Document of specifications shall include specifications for raw materials, packaging materials, intermediate products, bulk products and finished products.

10.2.1 *Raw Material Specifications*

10.2.1.1 Specifications for raw materials shall include:

10.2.1.1.1 material name/code designated by own company

10.2.1.1.2 material name/code designated by the supplier

10.2.1.1.3 material description, physical and chemical characteristics, and its microbiological standards, if any

10.2.1.1.4 reference monograph or pharmacopoeia or the method employed for testing the material

10.2.1.1.5 retest interval of the material in store, if required

10.2.1.1.6 storage requirements and other safety precautions

10.2.1.1.7 shelf - life of material

10.2.1.1.8 name of approved supplier and

10.2.1.1.9 date of issue

10.2.1.2 The raw material specifications are kept either separately or attached to the master production document.

10.2.2 *Packaging Material Specifications*

10.2.2.1 Specifications for packaging materials shall include:

10.2.2.1.1 material name/code desig-nated by own company

10.2.2.1.2 material name/code designated by the supplier

10.2.2.1.3 material description such as type of material, thickness, dimension, color, strength and printed text

10.2.2.1.4 technical drawing where applicable

10.2.2.1.5 reference monograph or pharmacopoeia or the method used for testing the material

10.2.2.1.6 retest interval of the material in store, if required

10.2.2.1.7 storage requirements and other safety precautions

10.2.2.1.8 shelf - life of material, if any

10.2.2.1.9 name of approved supplier and

10.2.2.1.10 date of issue

10.2.2.2 The packaging material specifications are kept either separately or attached to the master production document.

10.2.3 ***Specifications for Intermediate Products, Bulk Products and Finished Products***

10.2.3.1 Specifications for intermediate products, bulk products and finished products, according to its dosage form and stage of manufacturing shall include:

10.2.3.1.1 product name/code

10.2.3.1.2 dosage form and strength of product

10.2.3.1.3 product description, physical and chemical characteristics of the product and its microbiological standard, if any

10.2.3.1.4 reference monograph or pharmacopoeia or the method used for testing

10.2.3.1.5 physical properties such as fill weight or volume and their tolerance limits, pH, viscosity, density, hardness, friability, disintegration time and the dissolution rate, if required

10.2.3.1.6 the finished product specification should also specify the description of

the product presentation including the pack size

10.2.3.1.7 shelf-life of the product and

10.2.3.1.8 storage requirements and other safety precautions

10.2.3.2 The specifications for intermediate product, bulk product and finished product should be kept either separately or attached to the master production document.

10.3 *Production Documents*

10.3.1 *Master Batch Production Record*

10.3.1.1 A master production document should include the product name, dosage form, strength and description, the writer's name and department, name of verifier and list of document distribution.

10.3.1.2 The master batch production record should contain the following data:

10.3.1.2.1 general information des-cribing the product and the type of packaging material to be used or its alternative, statement of the product stability, safety precautions during storage and other precautions to be taken during processing and packaging of the product

10.3.1.2.2 product composition or formula for one dosage unit as well as for a sample of size

10.3.1.2.3 a complete list of raw materials whether they remain unchanged or become altered during processing

10.3.1.2.4 reference to the specification of raw materials

10.3.1.2.5 a complete list of packaging materials

10.3.1.2.6 reference to the specification of packaging material

10.3.1.2.7 processing and packaging procedures

10.3.1.2.8 list of equipment which may be used for processing and packaging

10.3.1.2.9 in-process control during processing and packaging and

10.3.1.2.10 product shelf-life

10.3.2 ***Master Processing Procedure***

10.3.2.1 A master processing procedure is a document from which copies are made for use in the processing of individual batches of product.

10.3.2.2 The master processing procedures shall outline a complete and detailed procedure and instruction for processing a product. It shall include the required in-process control that shall be performed by production and quality control staff, safety precautions and specific conditions that shall be applied throughout the process and during storage of intermediate and bulk product. The master processing procedure shall provide a blank space or form for recording the processing data. The master processing procedure shall be prepared, dated and signed by the production manager, and independently checked, dated and countersigned by the quality control manager.

10.3.2.3 The master processing procedure should include the following:

10.3.2.3.1 product name, dosage form and strength

10.3.2.3.2 a complete list of raw materials, designating the names and codes which specify their quality characteristics such as their monograph references

10.3.2.3.3 quantity of each active and inactive material expressed in a metric system unit of measurement for one dosage unit or batch size

10.3.2.3.4 statement of calculated overage of a raw material used in the process

10.3.2.3.5 permissible quantity of a product residue which may be added to the batch in process

10.3.2.3.6 numbers of different batches of lot of an active or inactive raw material which may be used in a batch of product

10.3.2.3.7 statement of the theoretical yield and percentage limits of the actual yield and

10.3.2.3.8 process location and equipment to be used

10.3.3 ***Master Packaging Procedure***

10.3.3.1 A master packaging procedure is a document from which copies are made for use in the packaging of individual batches of product.

10.3.3.2 The master packaging procedure shall outline a complete and detail procedure and instructions for packaging a product including the required in-process control which shall be performed by production and quality control staff, safety precautions and specific conditions that shall be applied through the packaging operation. The master packaging procedure shall provide a blank space or form for recording the packaging data. The master packaging procedure shall be prepared, dated and signed by the production manager, and independently checked, dated and countersigned by the quality control manager.

10.3.3.3 The master packaging procedure shall include the following:

10.3.3.3.1 product name, dosage form and strength and description of bulk product

10.3.3.3.2 a description of containers, closures and other packaging materials including a specimen of the product label and other labeling material which are signed and dated by the authorized person to approved such labeling

10.3.3.3.3 procedure for reconciliation of the issued quantities of bulk product and packaging materials with the number of unit packs produced

10.3.3.3.4 statement of the theoretical yield and percentage limits of the actual yield and

10.3.3.3.5 packaging line and equipment to be used

10.3.4 ***Batch Processing Record***

10.3.4.1 For each batch of product, a batch processing record shall be prepared. The record shall contain a complete information of the processing and control of the batch. The batch processing record form is reproduced from its master processing procedure and shall be checked for accuracy, dated and signed by the production manager.

10.3.4.2 The batch processing record shall show that each step of processing has been accomplished and include the following data:

10.3.4.2.1 batch number

10.3.4.2.2 dates of commencement and completion of processing and any significant intermediate stages

10.3.4.2.3 identity of major equipment and lines or location used

10.3.4.2.4 actual weight or volume and the lot or batch number of each raw material used in the process, and the signatures of the persons checking and counter-checking the dispensing of the materials as well as processing the batch

10.3.4.2.5 batch number or clearance reference number and the quantity of any product residue or recovered material used in the process

10.3.4.2.6 in-process control and laboratory test results

10.3.4.2.7 actual yield and its percentage against the theoretical yield after each critical step of processing

10.3.4.2.8 any sampling performed during various steps of processing including the quantity taken

10.3.4.2.9 initials of the operator and supervisor who check each step of the process

10.3.4.2.10 detail of any deviation from the master processing procedure and approval for such deviation

10.3.4.2.11 signature and date of approval from an authorized person to signify that all steps of processing have been performed in accordance with the master processing procedure and any process deviation or yield discrepancy is adequately explained and

10.3.4.2.12 investigation of a specific process failure or yield discrepancy

10.3.5 ***Batch Packaging Record***

10.3.5.1 For each batch of product, a batch packaging record shall be prepared. The record shall contain a complete information of the packaging and control of the batch. The batch packaging record form is reproduced from its master packaging procedure and shall be checked for accuracy, dated and signed by the production manager.

10.3.5.2 The batch packaging record shall show that each step of packaging has been accomplished and contain the following data:

10.3.5.2.1 Batch number

10.3.5.2.2 dates of starting and finishing the packaging

10.3.5.2.3 identity of major equipment and lines or location used

10.3.5.2.4 actual quantity and lot or batch number of each packaging material and bulk product used, and signatures of the persons weighing or counting the quantity and performing the counter-check

10.3.5.2.5 in-process control test and results

10.3.5.2.6 record of cleaning of the equipment used for packaging

10.3.5.2.7 line clearance check by an authorized person before and after use of the line

10.3.5.2.8 actual yield and its percentage against the theoretical yield at the completion of packaging

10.3.5.2.9 samples of packaging materials used and their control records, including materials that are already coded

10.3.5.2.10 any sampling performed during various steps of processing including the quantity taken

10.3.5.2.11 initials of the operator and supervisor who perform and check each step of the packing

10.3.5.2.12 record of reconciliation and disposition of unused packaging materials

10.3.5.2.13 test reports of the finished product and

10.3.5.2.14 investigation of a specific process failure or yield discrepancy

10.4 *Quality Control Documents*

The documents required in quality control are quality control procedures and test methods. The procedure for sampling is a very important document in quality control; and record of analysis and test report. The records of stability test results are usually presented separately. A test report may take the form of certificates of analysis.

10.4.1 *Procedure for sampling*

The procedure for sampling shall outline the design and method of sampling which should be approved, signed and dated by an authorized person. The procedure shall include the following:

10.4.1.1 method of sampling including the sampling plan and standard used in the sampling plan

10.4.1.2 equipment and sample container to be used

10.4.1.3 precautionary measures to be taken during sampling including use of special clothing by the person taking the sample

10.4.1.4 name of person or unit authorized to take the sample

10.4.1.5 location of sampling

10.4.1.6 quantity of sample taken and

10.4.1.7 method sub-dividing the sample taken, if required

10.4.2 *Test Method*

The test method is a detailed procedure for sampling and testing of starting materials, intermediate, bulk and finished products against their specifications. The test method shall include the name of reagent for analysis, identification test and assay of the material

under test as well as the computation formula to obtain the analytical result.

10.4.3 ***Record of Sampling***

A record of sampling shall be prepared in accordance with the approved procedure for sampling.

10.4.4 ***Record of Analysis and Test Report***

10.4.4.1 A record of analysis and test report shall be prepared for each lot or batch of starting material, intermediate, bulk and finished product following the approved method of testing. The record of analysis and test report shall include the statement of release or rejection of the material or product, the date and signatures of the analyst and supervisor.

10.4.4.2 The record of analysis shall contain the following data:

10.4.4.2.1 date of testing/analysis

10.4.4.2.2 material name including the code number, if any

10.4.4.2.3 supplier's name

10.4.4.2.4 date of receipt of the material or product

10.4.4.2.5 original batch/lot number;

10.4.4.2.6 lot/batch number or control number assigned by quality control

10.4.4.2.7 quantity received and the number of containers

10.4.4.2.8 date of sampling and the quantity taken

10.4.4.2.9 reference method of testing or the monograph used for testing

10.4.4.2.10 test report with date and signature of the analyst and supervisor

10.4.4.2.11 statement of release or rejection from quality control with signature of the responsible person and the date

10.4.4.2.12 number assigned to the certificate to release or reject the product, if any and

10.4.4.2.13 reference number of previously issued certificate; if required

10.4.4.3 The certificate of analysis serves as a test report that shall contain the following data:

10.4.4.3.1 name and address of the manufacturer or organization issuing the certificate

10.4.4.3.2 certificate number

10.4.4.3.3 name, dosage form and strength of the product

10.4.4.3.4 date of receipt of the material or product

10.4.4.3.5 original batch/lot number;

10.4.4.3.6 lot/batch number or control number assigned by quality control

10.4.4.3.7 quantity received

10.4.4.3.8 date of sampling and the quantity taken

10.4.4.3.9 reference method of testing or the monograph used for testing

10.4.4.3.10 test result including its tolerance limits

10.4.4.3.11 statement of release or rejection with explanation where necessary

10.4.4.3.12 date and signature of the analyst, supervisor and quality control manager

10.4.4.3.13 number assigned to the certificate to release or reject the product and

10.4.4.3.14 reference number of previously issued certificate; if required

10.4.4.4 The record of stability test shall include the requirements outlined in No. 10.4.4.2. as well as the following:

10.4.4.4.1 description of the packaging materials used for the product

10.4.4.4.2 time frame of the stability study

10.4.4.4.3 storage condition such as temperature and humidity of the product under study

10.4.4.4.4 test result of the product under study after each time frame and

10.4.4.4.5 test result comparison to the product specification and the result obtained initially

10.5 *Warehouse and Distribution Documents*

The storage and distribution of drug products shall be documented. The most important documents in this area are inventory card and distribution record.

10.5.1 *Inventory Card*

An inventory card for each product shall be prepared. The card contains record of the quantity received, issued and balance stock of the starting material, intermediate product, bulk product or finished product at any time.

10.5.1.1 The inventory card shall contain the following data:

10.5.1.1.1 material or product name and code number

10.5.1.1.2 date of receipt and issuing or delivery

10.5.1.1.3 quantity received or issued and the balance stock

10.5.1.1.4 batch number of material or product

10.5.1.1.5 storage location and

10.5.1.1.6 status of material or product, whether under quarantine, released or rejected

10.5.1.2 It is recommended to use different colors of inventory card for each group of product like active material, excipient, packaging material, intermediate product, bulk product or finished product.

10.5.1.3 The inventory card shall follow the first-in-first-out (FIFO) principle. Deviation from this principle shall be for a short term and only when approved by an authorized manager.

10.5.2 *Record of Distribution of Finished Product*

10.5.2.1 The record of distribution covers distribution of finished product. The record shall be complete, up to date and

the progressive data of distribution can be easily followed and retrievable to enable the manufacturer to impose a drug recall quickly and effectively whenever it becomes necessary.

10.5.2.2 The record of distribution shall contain the following data:

10.5.2.2.1 name and address of consignee

10.5.2.2.2 delivery order date and number

10.5.2.2.3 name, dosage form and strength of the product

10.5.2.2.4 quantity delivered

10.5.2.2.5 product batch number

10.5.2.2.6 expiration date where applicable and

10.5.2.2.7 special storage requirements or precautionary measures to handle the product

10.5.2.3 The inventory of finished products shall be recorded in an inventory card as referred to No. 10.5.1.1

10.6 *Documents for Maintenance, Cleaning and Monitoring of Manufacturing Areas and Equipment*

The most important documents for maintenance, cleaning and monitoring of manufacturing areas and equipment are the procedures and records for maintenance and cleaning of equipment and rooms, for pest control and for monitoring airborne particles and/or viable microorganisms in specific areas.

10.6.1 *Procedure and Record for Maintenance and Cleaning of Equipment*

10.6.1.1 A procedure for maintenance and cleaning of each piece of equipment shall be available. This procedure shall include the job description and the maintenance schedule. The maintenance and cleaning of equipment, including the repair job and replacement of equipment parts shall be recorded.

10.6.1.2 A procedure for cleaning production equipment shall specify cleaning of the equipment prior to change of batch as well as change of product. The procedure shall include the method of cleaning and the tools and cleaning materials to be used. The cleaning operation shall be documented and become part of the batch record.

10.6.2 *Procedure and Record for Cleaning of Manufacturing Area*

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

10.6.3 *Procedure and Record for Pest Control*

A procedure for pest control shall be available. This procedure shall include the scope and schedule of pest control, the method of control, the tools and pesticide to be used, precautionary measures and the persons or units involved in the pest control. The pest control operation shall be documented.

10.6.4 *Procedure and Record for Monitoring Airborne Particles and Microorganisms*

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

10.7 *Documents for Specific Equipment*

The most important documents for specific equipment are operating and calibrating procedure for an equipment and record of use and calibration of equipment.

10.7.1 *Procedure for Operating a Specific Equipment*

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

10.7.2 *Procedure and Record of Calibration of a Specific Equipment*

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

10.8 *Procedure and Record of Self Inspection*

10.8.1 A procedure for self-inspecting the manufacturing facility and system shall be available. The procedure shall include the forms to be used and check list for self-inspection, team composition and the schedule of inspection.

10.8.2 A record of the self-inspection and its result shall be named. The record shall contain the team's evaluation and conclusion of the inspection and corrective actions to be taken as necessary.

10.9 *Guidelines and Records of Personnel Training on Good Manufacturing Practices*

10.9.1 A guideline on Good Manufacturing Practices training for personnel relevant to their duties and responsibilities shall be available.

10.9.2 The record shall contain the following data:

10.9.2.1 Date of training

10.9.2.2 Name of persons attending the training

10.9.2.3 Name of instructor, department or institute conducting the training

10.9.2.4 Training materials and training ads

10.9.2.5 Demonstration provided; if any, and

10.9.2.6 Evaluation of trainee

10.10 *Documents for Handling of Product Complaints, Product Recall, Returned Products and Destruction of Products*

10.10.1 **Procedure and Record for Product Complaints**

10.10.1.1 A procedure for handling product complaints and report of adverse reaction of product shall be available. This procedure shall include the definition of product complaint and adverse reaction, the type of complaint and report, method of handling and evaluation of the complaint and report.

10.10.1.2 The records of product complaints and adverse reaction reports shall contain the following data:

10.10.1.2.1 product name and batch number

10.10.1.2.2 type of complaint or report

10.10.1.2.3 source of complaint or report

10.10.1.2.4 sample of complaint or reported product

10.10.1.2.5 summary of complaint or report

10.10.1.2.6 result of investigation

10.10.1.2.7 evaluation of complaint or report and

10.10.1.2.8 response and follow-up action to the complaint or report

10.10.2 **Procedure and Record for Returned Products**

10.10.2.1 A procedure for handling returned products shall be available. The procedure shall specify the guidelines for making decision either to salvage, reprocess or destroy the returned product. Returned products, which cannot be reprocessed, shall be destroyed. The handling, disposition and follow-up actions of returned products should be documented and reported.

10.10.2.2 The procedure for handling returned products shall include:

10.10.2.2.1 identifying and recording the quality of returned drug product

10.10.2.2.2 holding the product in quarantine

10.10.2.2.3 investigation, test and analysis of the product by quality control

10.10.2.2.4 critical evaluation before the management decides whether the product may be reprocessed or not

10.10.2.2.5 additional test for a requirement of the reprocessed product

10.10.3 **Procedure and Record for Product Recall**

10.10.3.1 A procedure for recalling a batch or lot or all of a finished product from market distribution shall be available.

10.10.3.2 A record of product recall shall be made and properly documented. The record shall contain the following data:

10.10.3.2.1 product name, batch number and batch size

10.10.3.2.2 date of starting and completing the product recall

10.10.3.2.3 reason of recall

10.10.3.2.4 warehouse stock and distributed stock of the product being recalled at the start of recall

10.10.3.2.5 quantity of recall product returned from the market

10.10.3.2.6 source of returns

10.10.3.2.7 evaluations of product recall

10.10.3.2.8 follow-up actions to be taken and

10.10.3.2.9 report on the handling of product recall to the management and to the government authority, if required

10.10.4 ***Procedure and Record of Destruction of Rejected Material or Product***

10.10.4.1 A procedure for destruction of rejected materials or products shall be available. The procedure shall include precautionary measures to prevent pollution of the environment and actions taken to prevent misuse of the materials or products by unauthorized persons.

10.10.4.2 A record of rejected material or product destruction shall be made. The record shall contain the following data:

10.10.4.2.1 product name, batch number and quantity of rejects

10.10.4.2.2 source of rejected material or product

10.10.4.2.3 method of destruction and

10.10.4.2.4 persons performing and witnessing the destruction

Section 11 *SELF INSPECTION*

The purpose of self-inspection is to evaluate the manufacturer's compliance with Good Manufacturing Practices on all aspects of production and quality control. The self-inspection program shall be designed to detect any shortcoming towards the implementation of Good Manufacturing Practices and to recommend the necessary corrective actions. Self-inspection shall be performed routinely. All recommendations for corrective actions shall be implemented. A team consisting of personnel who can evaluate the implementation of Good Manufacturing Practices objectively shall be appointed. The procedure and record for self-inspection shall be documented.

11.1 ***Items for Self Inspection***

A checklist for self-inspection shall be established to provide a minimum and uniform standards of requirements. The list shall include questionnaires on Good Manufacturing Practices requirements covering the following items:

11.1.1 personnel; premises including personnel facility

11.1.2 storage of starting materials and finished products

11.1.3 equipment

11.1.4 production

11.1.5 quality control

11.1.6 documentation and

11.1.7 maintenance of building and equipment

11.2 *Team of Self Inspection*

Management shall appoint a team of self-inspection consisting of at least three members who are experts in their own fields and familiar with Good Manufacturing Practices. The members of the team may be appointed from inside or outside the company. Each member shall be independent in performing the inspection and evaluation.

11.3 *Coverage and Frequency of Self Inspection*

Self-inspection may be conducted by part of unit depending on the company requirement, however, a complete self inspection shall be conducted at least once a year.

11.4 *Self Inspection Report*

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

11.4.1 self-inspection report

11.4.2 evaluation and conclusion and

11.4.3 recommended corrective actions

11.5 **Follow - up Action**

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

Section 12 *GUIDELINES FOR HANDLING OF PRODUCT COMPLAINT, PRODUCT RECALL AND OR RETURNED PRODUCT*

12.1 *Product Complaint and Report*

A product complaint and report may relate to the quality, adverse reaction or other therapeutic effect of the product. All complaints and reports shall be thoroughly investigated and evaluated. There shall be a follow-up action after investigation and evaluation of the complaint and report are completed.

12.1.1 A product complaint and report may be due to:

12.1.1.1 a complaint about quality whether physical, chemical or biological defect of the product or its packaging

12.1.1.2 a complaint or report of adverse reaction like allergy, toxicity, fatal or near fatal reaction and other medical reaction and

12.1.1.3 a complaint or report of the product therapeutic activity such as the product lack of efficacy or poor clinical response

12.1.2 A system for handling product complaint shall be designed and include written procedures and indicate the responsibility of persons through whom the complaints are to be channeled. A record shall be made for all product complaints and reports received.

12.1.3 The relevant unit or department according to the type of complaint or report received shall handle product complaints and reports.

12.1.4 Each complaint and report shall be thoroughly investigated and evaluated including:

12.1.4.1 a review of all information on the complaint or report

12.1.4.2 an inspection or test on the complaint sample received and if necessary on the retained sample of the same batch and

12.1.4.3 a review of all data and documentation including the batch record, distribution record and test report of the product complaint or report

12.1.5 ***Follow-up Action***

A follow-up action shall be taken after investigation and evaluation of the product complaint and report. The action may include:

12.1.5.1 corrective action where applicable

12.1.5.2 recall of the batch or all the finished products

12.1.5.3 other appropriate action

12.1.6 The handling of product complaints and reports including results of their evaluation of investigation and the follow-up actions taken should be recorded and reported to the relevant management or department and to the government authority.

12.2 *Product Recall*

A product recall is a process of withdrawing one or more batches or all of a certain product from market distribution. A product recall is instituted following discovery of a quality defect or if there is a report of serious adverse reaction of a product which may cause health risk. Total withdrawal of a product from market distribution may result in a suspension or discontinuation of manufacturing of the product.

12.2.1 *Decision for Recall*

12.2.1.1 Decision to recall a product may be initiated by the manufacturer or under instruction of the government authority.

12.2.1.2 Decision to recall a product shall come internally from the quality control manager and the company management.

12.2.1.3 Decision to recall may involve one or more batches or all of the finished product.

12.2.1.4 Decision to recall a product may result in suspension or discontinuation of manufacturing of the product.

12.2.2 *Institution of Recall*

12.2.2.1 A product recall shall be instituted immediately after discovery of a quality defect or receiving report of adverse reaction of the product.

12.2.2.2 Products with high health risk should be prevented from further usage by having them under embargo as well as recalling the products immediately. The recall point shall reach the consumer level.

12.2.2.3 The manufacturer documentation system for product recall shall ensure that recall and embargo have been adequate quickly, effectively and completely carried out.

12.2.2.4 Procedure and guideline to recall a product shall be established to enable the recall and embargo be quickly and effectively carried out from all points distribution.

12.2.2.5 The record and report of product recall including the result of product recall and embargo action should be properly documented.

12.3 ***Returned Product***

A returned product is a finished product which is already in distribution and returned to the manufacturer due to complaint, damage, expiration, validity or other reasons such as the condition of the container or package which may cast doubt on the product identity, quality, quantity and safety. The manufacturer shall establish a procedure for holdings, investigating and analyzing the returned product and deciding whether the product may be reprocessed or shall be destroyed after a critical evaluation is made.

Based on the evaluation, the returned products are categorized as follows:

12.3.1 returned products which still meet their specifications and therefore may be returned to inventory

12.3.2 returned products which may be reprocessed and

12.3.3 returned products which do not meet their specifications and cannot be reprocessed

PART 3. ***STERILE PRODUCTS***

INTRODUCTION

These guidelines do not replace any of the sections in Parts One and Two but stress specific points for the manufacture of sterile preparations to minimize the risks of microbiological, particulate and pyrogen contamination.

Section 1 General Characteristics

1.1 The production of sterile preparations should be carried out in clean areas, entry to which should be through air locks for personnel and or for goods. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of an appropriate efficiency.

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

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

Table 1

	Maximum number of Particles permitted per m^3		Maximum number of viable microorganisms
Grade	0.5-5 µm	>5 µm	Permitted per m^3
A (laminar-airflow workstation)	3500	None	Less than 1
B	3500	None	5
C	350000	2000	100
D	3500000	20000	500

1.4 To obtain air of the required characteristics, methods specified should be used. It should be noted that :

1.4.1 Laminar-airflow systems should provide a homogenous air speed of about 0.30 m/s for vertical flow and about 0.45 m/s for horizontal flow but precise air speeds would depend on the type of equipment.

1.4.2 In order to reach the B, C, and D air grades, the number of air changes should generally be higher than 20 per hour in a room with a good airflow pattern and appropriate HEPA (high-efficiency particulate air) filters.

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

1.4.4 The guidance given for the maximum permitted number of particles corresponds approximately to the United States Federal Standard 209 E (1992) as follows: Class 100 (grades A & B), Class 10,000 (grade C), and Class 100,000 (grade D). It may not always be possible to demonstrate conformity with particular air standards at the point of fill when filling is in progress, owing to the generation of particles or droplets from the product itself.

1.5 Each manufacturing operation requires an appropriate air cleanliness level in order to minimize the risks of particulate or microbial contamination of the product or materials being handled. Section 1.6 gives the minimum air grades required for different manufacturing operations. The particulate and microbiological conditions given in Table 1 should be maintained in the zone immediately surrounding the product whenever the product is exposed to the environment. These conditions should also be achieved throughout the background environment if no personnel are present in the processing area, and if the standards fall for any reason it should be possible to recover the conditions after a short " clean-up" period. The utilization of absolute-barrier technology and automated systems to minimize human interventions in processing areas can produce significant advantages in ensuring the sterility of manufactured products.

1.6 Manufacturing operations are divided into three categories: first, those in which the preparation is sealed in its final container and terminally sterilized; second, those in which the preparation is sterilized by filtration; and third, those in which the preparation can be sterilized either by filtration or terminally and consequently must be produced from sterile starting materials in an aseptic way. Area grades as specified in 1.6.1- 1.6.3, must be selected by the manufacturer on the basis of validation runs (e.g. sterile media fills).

1.6.1 Terminally sterilized products: Solutions should generally be prepared in a grade C environment in order to give low microbial and particulate counts, suitable for immediate filtration and sterilization. Solution preparation could be allowed in a grade D environment if additional measures were taken to minimize contamination, such as the use of close vessels. For parenterals, filling should be done in a laminar-airflow workstation (grade A) in a grade C environment. The preparation of other sterile products, e.g. ointments, creams, suspensions, and emulsions, and filling of

containers should generally be done in a grade C environment before terminal sterilization.

1.6.2 Sterile filtered products: The handling of starting materials and the preparation of solutions should be done in a grade C environment. These activities could be allowed in a grade D environment if additional measures were taken to minimize contamination, such as the use of closed vessels prior to filtration. After sterile filtration, the product must be handled and dispensed into containers under aseptic conditions in a grade A or B area with a grade B or C background respectively.

1.6.3 Other sterile products prepared from sterile starting materials in an aseptic way. The handling of starting materials and all further processing should be done in a grade A or B area with a grade B or C background respectively.

Section 2 Personnel

2.1 Personnel required to work in clean and sterile areas should be selected with care to ensure that they may be relied upon to observe the appropriate disciplines and are not subject to any disease or condition which would present any microbiological hazard to the product.

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

2.3 All personnel, including those concerned with maintenance employed in such areas should receive regular training in the disciplines relevant to the correct manufacture of sterile products, including reference to hygiene and at least the basic elements of microbiology.

Section 3 Clothing

3.1 Personnel entering clean or sterile areas should change into special garments, which include head, and foot wears. These garments should shed virtually no fibres or particulate matter, and retain particles shed by the body. They should be comfortable to wear, and loose fitting to reduce abrasion. The garments should be restricted for use only in the relevant clean or sterile areas.

3.2 In aseptic processing area personnel should wear sterilized single or two-piece trouser-suits, gathered at the wrists and ankles and with high necks. Headgear should totally enclose hair and beard and be tucked into the neck of the suit. Footwear should totally enclose the feet, and trouser-bottoms should be tucked inside the footwear. Cleaned and sterilized protective garments should be provided each time a person enters a sterile area. Powder-free rubber or plastic gloves should be worn with the garment sleeves tucked inside the gloves. Protective eye protection should be worn. A non-linting facemask should also be comfortable to wear and discarded at least each time the sterile area is left.

3.3 Outdoor clothing should not be brought into the clean areas. Personnel entering the changing room should already be clad in standard factory working clothes. Changing and washing should follow a written procedure.

3.4 Wristwatches and jewelries should not be worn. Cosmetics should not be used.

3.5 Clean and aseptic processing area clothing should be laundered and sterilized. Separate laundry facilities for such clothing are desirable. Washing and sterilization operations should follow Standard Operating Procedure.

Section 4 Cleanliness and Hygiene

4.1 Sterile product processing areas should be cleaned frequently and thoroughly in accordance with a written program. Where disinfectants are used, different types should be employed in rotation to discourage the development of resistant strains of microorganisms. Monitoring should be regularly undertaken in order to detect the emergence of resistant strains of microorganisms.

4.2 Disinfectants and detergents used should be monitored for microbial contamination. Dilutions should be kept in previously cleaned containers and should not be stored unless sterilized. Partly emptied containers should not be refilled.

4.3 Areas should be frequently monitored microbiologically by means of exposure plates, surface sampling, air sampling or other appropriate methods. The monitoring should be performed while normal production operations are in progress. When aseptic operations are performed, monitoring should be frequent to ensure that the environment is within specification. The results of monitoring should be considered when batches are assessed for approval.

Section 5PREMISES

5.1 The surfaces of walls, floors and ceilings should be smooth, impervious and unbroken in order to minimize the shedding or accumulation of particulate matter, and to permit the repeated application of cleaning agents and disinfectants where used.

5.2 To reduce accumulation of dust and to facilitate cleaning, there should be no uncleanable recesses and a minimum of projecting ledges, shelves, cupboards, equipment, fixtures and fittings. Coving should be used where walls meet floors and ceilings in sterile areas and other clean areas.

5.3 Ceilings should be adequately sealed to prevent contamination from the space above them.

5.4 Pipes and ducts should be installed so that they do not create recesses that are difficult to clean. They should be sealed into walls through which they pass.

5.5 Drains should be avoided wherever possible and excluded from sterile areas unless essential. Where installed they should be fitted with effective, easily cleanable traps and with air breaks to prevent back-flow. Any floor channels should be open, shallow enough and easily cleanable and be connected to drains outside the area in a manner that prevents access to microbial contaminants.

5.6 Sinks should be excluded from aseptic processing. Any sink installed in other clean areas should be of stainless steel, without overflow, and be supplied with water of at least potable quality.

5.7 Room temperature and humidity should be maintained at a level that will not cause excessive sweating of operators clad in protective garments.

5.8 Access to clean and sterile areas should be restricted to authorized persons who enter only through changing rooms where normal factory working clothes are changed with special protective garments.

5.9 Changing rooms should be designed as airlocks and used to provide separation of the different stages of changing, minimizing microbial and particulate contamination of protective clothing. They should be effectively flushed with filtered air. Hand washing facilities should be provided only in changing rooms, not in areas where aseptic work is done.

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

5.11 Conveyor belts should not pass through walls enclosing sterile areas. They should end at the wall, products passing onwards across at stationary surface.

Section 6 Equipment

6.1 Equipment should be designed and installed so that it may be easily cleaned, disinfected or sterilized as required.

6.2 As far as possible, equipment fittings and services should be designed and installed so that maintenance and repair can be carried out without additional personnel having to enter the clean or sterile areas.

6.3 Recording apparatus should be accurately calibrated on installation and thereafter checked at scheduled intervals.

6.4 All equipment, including sterilizers, air-filtration systems, and water-treatment systems including stills, should be subject to planned maintenance, validation and monitoring; its approved use following maintenance work should be documented.

6.5 A filtered air supply should maintain a positive pressure relative to surrounding areas under all operational conditions and flush the area effectively. Moreover, particular attention should be paid to the protection of the zone of greater risk, that is, the immediate environment to which the product and the cleaned components in contact with it are exposed. Decontamination facilities and the treatment of air leaving a clean area maybe necessary for some operations.

6.6 It should be demonstrated that airflow patterns do not present a contamination risk, for example care should be taken to ensure that airflows do not distribute particles from a particle-generating person, operation, or machine to a zone of higher product risk.

6.7 A warning system should be included to indicate failure in the air supply. An indicator for pressure difference should be fitted between areas where this

difference is important and the pressure difference should be regularly recorded.

6.8 Consideration should be given to restricting unnecessary access to critical filling areas, e.g. grade A filling zones, by the use of a physical barrier.

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

6.10 Whenever possible, equipment used for processing sterile products should be chosen so that it can be effectively sterilized by steam or dry heat or other methods.

6.11 When equipment maintenance is carried out within the clean area, clean instruments and tools should be used, and the area should be cleaned and disinfected where appropriate before processing recommences, if the required standards of cleanliness and or asepsis have not been maintained during the maintenance work.

6.12 Water- treatment plants should be designed, constructed, and maintained so as to ensure the reliable production of water of an appropriate quality. They should not be operated beyond their designed capacity. Water should be produced, stored, and distributed in a manner that prevents microbial growth, e.g. by constant circulation at 80^0C or not more than 4^0C.

Section 7 PRODUCTION

7.1 The design features for facilities for manufacture of sterile products should ensure that the areas in which product contact components are to be prepared and which products are to be processed, filled and sealed should be segregated from other manufacturing areas and not used for any other procedures. These areas should be designed, operated and managed as to minimize microbial and particulate contamination of products throughout processing. The design of sterilizing facilities should preclude mix-up between untreated and treated (sterilized) materials.

7.2 Cleanrooms should be effectively flushed with air supplied under positive pressure and delivered through HEPA air filters located where the air enters the processing environment. Air inlets should be remote from the air outlets in order to achieve effective flushing of the room space to allow critical operations to be located in the least contaminated stream of air. Air outlets should be at low level.

7.3 Cleanrooms should contain the minimum of " dead" space, i.e. space not effectively flushed with clean air, the minimum of obstructions to flow of clean air, such as fittings, ledges and shelves and no extraneous equipment. The design materials and construction should prevent access of which has not been filtered.

7.4 Cleanrooms should be provided with suitable anterooms or equivalent separation facilities through which staff or articles may enter or leave the area. Suitable changing and wash facilities should be provided in these anterooms. The change areas should be arbitrarily divided into a " dirty section" (adjacent to the entry to the cleanroom) to assure proper gowning procedures. A " step-

over" bench should be made available to assist in change procedures and to provide the physical division between each end of the change area.

7.5 There should be separate rooms with appropriate grade of clean filtered air for container and closure preparation and for batch compounding.

7.6 There should be a "cascade" of air pressure values between the sterile manufacturing area and adjacent areas. The design of the facility should assure that all areas supplied with HEPA filtered are positive air pressure differential to ambient air pressure and the sterile filling area is maintained at a positive pressure differential to immediately adjacent areas. There are specific air cleanliness requirements for different activities conducted in a cleanroom suite of rooms.

7.7 The manufacture of aseptic fill sterile product (includes lyophilization processes) should utilize a double barrier system. The double barrier system of manufacture assures sterility of the finished product by filling, capping/ sealing the sterile filtered product in a special work zone environment of class 100 air cleanliness Air supplied by HEPA filters. The class 100 work zone (the 1st barrier) is protected by enclosing the work zone with physical barriers to assure the laminar flow characteristics of supplied air are maintained. The work zone is housed in a room supplied with class 10,000 air (the 2nd barrier). Operators operating in an aseptic sterile manufacturing area need to be specially gowned in non-shedding, non-aspirating clothing to assure protection of the product and the filling environment from microbial and particulate contamination.

7.8 The manufacture of terminally sterile products should be carried out in a class 10,000 air cleanliness environment.

7.9 Where a company is utilizing the one facility for both aseptic and terminally sterilized product then the company should operate to the higher standard of cleanliness at all times.

7.10 Segregated areas are required for the following operations:

7.10.1 depacking component from containers

7.10.2 equipment and component washing

7.10.3 processing

7.10.4 filling and sealing of immediate containers

7.10.5 airlock or other separate area, connecting gowning and filling room

7.10.6 gowning room for changing into sterile working clothes prior to entering the sterile area

Section 8 Processing

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

8.2 Preparations containing live microbiological organisms should not be made or containers filled in areas used for the processing of other pharmaceutical products; however, vaccines of dead organisms or of bacterial extracts maybe

dispensed into containers, after validated inactivation and validated cleaning procedures, in the same premises as other sterile pharmaceutical products.

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

8.3.1 They should simulate as closely as possible actual operations, taking into account such factors as complexity of operations, number of personnel working, and length of time.

8.3.2 The medium or media selected should be capable of growing a wide spectrum of microorganisms, including those that would be expected to be found in the filling environment.

8.3.3 They should include a sufficient number of units of production to give a high degree of assurance that low levels of contamination, if present would be detected.

It is recommended that at least 3000 units of production be included in each broth-fill trial. The target should be zero growth and anything above 0.1% of units contaminated should be considered unacceptable. Any contamination should be investigated. Broth fills should be repeated at regular intervals, and whenever a significant alteration in the product premises, equipment, or process warrants revalidation.

8.4 Care should be taken that validations do not harm the processes.

8.5 Water sources, water treatment equipment and treated water should be monitored regularly for chemical, microbial and pyrogen contamination. Records should be maintained of the results of the monitoring and of any remedial action.

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

8.7 The presence of containers and materials liable to generate fibers should be minimized in clean areas and avoided completely when aseptic work is in progress.

8.8 The interval between the washing and drying and the sterilization of components, bulk-product containers, and equipment, as well as between sterilization and use, should be as short as possible and subject to a time-limit appropriate to the validated storage conditions.

8.9 The time between the start of the preparation of a solution and its sterilization or filtration through a bacteria-retaining filter should be as short as possible. A maximum permissible time should be set for each product that takes into account its composition and the prescribed method of storage.

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

8.11 The microbiological contamination of products (" bioburden") should be minimal prior to sterilization. There should be a working limit on contamination immediately before sterilization that is related to the efficiency of the method to be used and the risk of pyrogens. All solutions, in particular large-volume parenterals, should be passed through a microrganism-retaining filter, if possible immediately before the filling process. Where aqueous solutions are held in sealed vessels, any pressure-release outlets should be protected, e.g. by hydrophobic microbial filters.

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

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

8.14 Water treatment plants should be designed, constructed, and maintained to ensure the reliable production of water of the required quality. They should not be operated beyond their designed capacity. The water should be produced, stored and distributed in such a manner as to discourage microbial growth.

8.15 Distilled water intended for further processing or sterilization should not stand for more than 24 hours unless special precautions are taken, such as storage at least at 70^0C, to prevent both the growth of bacteria and the consequent development of pyrogens.

8.16 Where water and solutions are held in sealed vessels, any pressure relief outlets should be protected by hydrophobic microbial air filters.

8.17 When a new aseptic process is introduced, when any significant change is made in such a process or in the equipment, when staffs are being trained and at a regular intervals thereafter, the efficacy of aseptic procedures should be validated.

Section 9 Sterilization

9.1 Sterilization can be effected by moist or dry heat, by ethylene oxide, by filtration with subsequent aseptic filling into sterile final containers, or by radiation with ionizing radiation. Each method has its particular applications and limitations.

9.2 If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination from them.

9.3 There should be a clear means of differentiating products that have not been sterilized from those sterilized. Each basket, tray or other carrier of product or component should be clearly labeled with the material name, its batch number and an indication of whether or not it has been sterilized.

9.4 A brief summary of sterilizing parameters for each type of sterilization is as follows:

steam sterilization - temperature/ time/pressure

9.4.1 dry heat sterilization - temperature/ time

Note: Dry heat sterilization cycles maybe modified to also meet conditions for depyrogenation of components where necessary.

9.4.2 Ethylene Oxide sterilization - Ethylene Oxide concentration/Temperature/Humidity/Pressure/ Biological indicators

9.4.3 Gamma Irradiation- dose of gamma rays/time

9.4.4 Electron beam sterilization - dose of radiation/time

9.5 ***Heat Sterilization***

9.5.1 Each heat sterilization cycle should be recorded on a temperature/time chart or by other suitable automatic means. The time-temperature record should form part of the batch record. Chemical or biological indicators may be used in addition, but should not take the place of physical controls.

9.5.2 After the high temperature phase of a heat sterilization cycle, precautions should be taken during cooling to prevent contamination of a sterile load by non-sterile air entering the sterilization unit.

9.6 ***Sterilization by Moist Heat***

9.6.1 This method is suitable for water-wettable materials and aqueous solutions. Other materials should be sterilized by other methods.

9.6.2 Moist heat sterilization is achieved by exposure to saturated steam under pressure in a suitably designed chamber. In these circumstances there is an exact relationship between the steam temperature and pressure, but the pressure is used solely to obtain the required temperature and otherwise contributes nothing to the sterilization process. The time, temperature and pressure should be used to control and monitor the process.

9.6.3 Items to be sterilized, other than aqueous products in sealed containers, should be wrapped in a material which allows the removal of air and penetration of steam, and which under normal conditions does not permit recontamination by microorganisms after sterilization.

9.6.4 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.

9.7 ***Sterilization by Dry Heat***

9.7.1 Dry heat is suitable for sterilizing equipment, non-aqueous liquids and other materials that can withstand the temperatures required.

9.7.2 Heating should be carried out in an oven or other equipment that will achieve sterilizing conditions throughout the load. Air supply and exhaust systems to the sterilizing oven should be equipped with suitable filters.

9.8 ***Sterilization by Filtration***

9.8.1 Sterilization by filtration should not be used when sterilization by heat is possible.

9.8.2 Solutions or liquids can be sterilized by filtration through a sterile filter or nominal pore size of 0.22 micron or with at least equivalent microorganism retaining properties, into a previously sterilized container.

9.8.3 The integrity of the filter assembly should be checked by an appropriate method, such as bubble-point pressure test, or forward flow pressure test immediately before and after use. Results of these filter-integrity checks should be recorded in the batch record.

9.8.4 The filter should not adversely affect the solution by removal of ingredients from it, or by release of substances into the solution.

9.8.5 Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration using a sterilized microorganisms retaining filter, immediately prior to filling, is also advisable.

9.8.6 The period of time a sterilizing filter is in use should be limited to ensure that there is no microbial growth in the filter.

9.9 ***Sterilization by Ethylene Oxide***

9.9.1 The efficacy of ethylene oxide as a sterilant depends upon its concentration, temperature and humidity, time of exposure and extent of microbial contamination. Where other methods of sterilization are possible they should be used in preference to ethylene oxide method.

9.9.2 Each sterilizing cycle should be monitored with suitable biological indictors, distributed throughout each load. The information from these should be part of the batch record.

9.9.3 After exposure, materials should be held under adequate ventilation to allow any ethylene oxide, and its reaction products to diffuse. Care should be taken to prevent recontamination of the sterilized goods, and a recorded check made that all biological indicators have been removed from the load.

9.9.4 During each sterilization cycle records should be made of the time taken to complete the cycle, pressure, temperature, gas concentration and the humidity within the chamber.

9.9.5 The pressure, temperature and relative humidity should be controlled and recorded throughout a cycle on a chart, or by other

suitable automatic means. These records should be part of the batch record.

9.10 ***Sterilization by Radiation***

9.10.1 Radiation sterilization is used mainly for the sterilization of heat sensitive materials and products. This method is permissible only when the absence of deleterious effects on the product has been confirmed.

9.10.2 The radiation employed may be gamma rays from a radioisotope (e.g. Cobalt 60) or high-energy electrons (beta radiation) from an electron accelerator.

9.10.3 Treatment by irradiation may be carried out by the pharmaceutical manufacturer or by an operator of a radiation facility under contract (a "contact manufacturer"), both of whom must hold an appropriate manufacturing authorization.

9.10.4 The pharmaceutical manufacturer bears responsibility for the quality of the product including the attainment of the objective of irradiation.

9.10.5 During the sterilization procedure the radiation dose should be monitored. For this purpose, established dosimetry procedures should be used, giving a quantitative measurement of the dose received by the product itself. Biological indicators should only be used as additional control. The information obtained should form part of the batch record.

9.10.6 Care should be taken to distinguish between materials that have been irradiated and those that have not. Design of plant and the use of radiation-sensitive discs can ensure this.

9.10.7 The number of containers received irradiated and dispatched should be reconciled with each other and with the associated documentation. Any discrepancy should be reported and resolved.

9.10.8 The irradiation plant operator should certify in writing the range of doses received by its irradiated container within a batch or delivery.

9.10.9 Process and control records for each irradiation batch should be checked and signed by a nominated responsible person and should be retained. The method and place of retention should be agreed between the plant operator and the holder of the marketing authorization.

9.10.10 Microbiological monitoring is the responsibility of the pharmaceutical manufacturer. It may include environmental monitoring where product is manufactured and pre-irradiation monitoring of the product as specified in the marketing authorization.

Section 10 Validation requirements for sterilization processes

Validation Studies of sterilization processes should be conducted based on documented loading patterns for product and equipment for each different method of sterilization method employed.

10.1 Terminally sterilized products:

10.1.1 Facilities and processing activities for preparation of product before sterilization must assure that the bioburden of the bulk product, contact product components and related processing equipment used in manufacture must have low bioburden levels and this level must be uniform throughout the batch.

10.1.2 Minimum sterilizing conditions are uniformly attained throughout the batch and the application of the "sterilizing agent" to the batch is also uniformly achieved.

10.1.3 The parameters of the sterilizing cycle are routinely monitored and controlled for each sterilization cycle, records of this monitoring should form part of the batch record.

10.1.4 All loading configurations of product, components and equipment within the sterilizing chamber have to be standardized and documented and the sterilization process for each load configuration should be validated.

10.1.5 New (prospective) validation studies should be carried out whenever there is a significant change in equipment, processing, loading configuration, product or packaging.

10.2 Aseptic product manufacturing procedures, equipment and environments should be validated for the overall performance by test runs with suitable sterile growth media, at the initial qualification stage and at regular intervals thereafter. In the case of liquid processing the sterile growth media should be soybeancasein digest media and the filled containers should be incubated at 32oC + or – 2oC for at least 14 days. Full microbiological media test controls should be carried out.

10.2.1 For each container type filled, at least 3000 typical containers should be subjected to the media fill exercise under normal processing conditions but also including "worst case" situations.

10.2.2 Initial validation of aseptic processing should involve three media fills, each not less than 3000 units. No growth should be observed in the incubated units: however manufacture of products need not be terminated if a contamination rate less than 0.1% (3 units in 3000 filled) is achieved.

10.3 For heat sterilization, whether by moist heat or dry heat, validation studies should include the following minimum requirements:

10.3.1 Bioburden studies on representative samples of the filled bulk product (before sterilization).

Heat distribution studies for each sterilizer load configuration, to identify “cold spots” within the sterilizer chamber. Distribution studies should include adequate calibrated temperature sensors to allow the temperature profile for the chamber to be determined.

Heat penetration studies for each container size. The studies should be designed to determine the time to bring the contents of

the container to the prescribed sterilizing temperature. Two monitors should be included in each container used: a biological indicator and a temperature sensor.
It is important that some of the containers in this study be placed at the “cold spots” of the chamber.

10.3.2 Determination of the Fo values (or in the case of the dry heat sterilization Fh values) using the same number and position of the temperature sensors as described in the heat penetration studies.

10.4 For gas (Ethylene Oxide and Ethylene Oxide plus dilution gases) sterilization validation studies should include the following minimum requirements:

10.4.1 Pre-sterilization bioburden studies of representative samples of the batch

10.4.2 Temperature distribution studies on each sterilizer chamber for each load configuration

10.4.3 Microbiological challenge testing used biological indicators placed in the “ most difficult- sterilized site within product packs and distributing these challenges packs throughout the load. It is generally accepted that sufficient indicators should be used to provide at least one indicator for 3 cubic meters of product load, but no fewer that 10 B.I. ‘s. This location should be documented.

10.4.4 Measurement of relative humidity (at least in the absence of sterilant gas).

10.4.5 Studies on the efficiency of the aeration and occurrence of toxic residues.

10.5 For gamma radiation sterilization, validation studies should include the following minimum requirements:

10.5.1 dose mapping of the radiation cycle for different product densities

10.5.2 calibration of the timers, dosimeters and spectrophotometers for recording and monitoring validation cycles

Section 11 Water

11.1 Water used in production of sterile products including its storage and supply system should be controlled to assure that it would meet appropriate specifications for each operation.

11.2 Water for injection should be produced either by distillation or other means that will produce the same quality.

11.3 Water for injection should be stored and continuously circulated at a temperature of at least 70^0C. A recording device should be used to monitor storage temperature. If water for injection is not circulated, it should be discarded after 24 hours.

11.4 Water for injection used in formulations should be controlled as a starting material.

11.5 Water for injection should be stored in clean, sterile, non-reactive, non-absorptive, non-additive containers and protected from contamination.

Section 12 Filtration of Pharmaceutical Products That Cannot Be Sterilized in their Final Container

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

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

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

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

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

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

Section 13 Finishing of Sterile Products

13.1 Where detergents or similar materials are used as a pre-rinse of containers, procedures should ensure that no residues would remain.

13.2 Containers should be rinsed at least with purified water. Personnel should not handle containers with bare hands. Once containers have been washed, dried and sterilized, they should be used within a specified time period.

13.3 Ampoules should be sealed by a “drawing-off” technique rather than by tip sealing.

13.4 The integrity of the seal of the final container should be checked by suitable procedures.

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

13.6 Where automatic, or electronic or photoelectric methods of inspection are used, the effectiveness of the equipment should be validated and its sensitivity monitored.

Section 14 Biological and Chemical Indicators

14.1 Biological and chemical indicators used alone are not acceptable as a proof that a sterilization process has been effective. They will show when sterilization has failed but not necessarily prove that the process has been successful.

14.2 Biological indicators are much less reliable than physical monitoring methods, except in ethylene oxide sterilization.

14.3 Strict precautions should be taken when handling biological indicators due to the hazard of introducing potential contaminants into an otherwise microbiologically clean area. They should be stored according to the indicator of manufacturer's specifications.

14.4 Chemical indicators are available for heat, ethylene oxide and radiation sterilization, usually in the form of adhesive tapes or patches color spot cards, small tubes or sachets. They change color as a result of chemical reaction brought about by the sterilization process. It is possible for the change to take place before the sterilizing time has been completed of plastic dosimeters used in radiation sterilization.

Section 15 Quality Control --- Test requirements

15.1 ***Test for Sterility***

15.1.1 Guidance on the minimum number of sample containers to be tested and on the standard method available for testing various types of preparations for aerobic and anaerobic bacteria, and for fungi should be given in standard test procedure.

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

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

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

15.1.3 The sterility test applied to the finished product should be regarded only as the last in a series of control measures by which sterility is

assured and can be interpreted only in conjunction with the environmental and batch processing records.

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

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

15.1.6 Records of sterility test results should be maintained.

15.2 ***Test for Pyrogens***

15.2.1 In the manufacture of any sterile product, careful consideration should be given to the need for testing raw materials, intermediate, bulk and finished products for pyrogens.

15.2.2 Water, whether as a raw material or finished product, is a particular risk of being pyrogenic. Water for injection should be tested for pyrogens when labelled “non-pyrogenic” or when filled into containers of over 10 ml.

15.2.3 Pyrogens become a more serious hazard in larger volume injections. Sterile products that have a single dose of more than 10 ml and are intravenously administered should be pyrogen free.

15.3 ***Sterility Test Sampling***

15.3.1 Samples taken for sterility testing should be representative of the finished batch and should represent the beginning, middle and end of the batch process. Sample size will be determined by pharmacopeial requirements and the method of sterilization and the controls / monitoring that was related to the sterilization process.

15.4 ***Sterility Test Method***

15.4.1 The methods mainly for sterility testing are membrane filtration and direct inoculation, however, membrane filtration is the preferred method. All equipment used in the test method should be sterilized by a validated sterilization procedure. All procedures related to the sterility test procedure should be conducted under the same conditions required for an aseptic manufacturing process i.e. a “double barrier” facility with operators correctly gowned to prevent contamination of the testing environment. Where the product to be tested has anti-microbial activity, the membrane used should have a hydrophobic edge to facilitate washing, to “ wash-out” the antimicrobial agent before introduction of media

15.5 ***Sterility Test Media***

15.5.1 The usual media are Fluid Thioglycollate medium and Soybean Casein Digest medium. The composition of the two media are so designed to support the growth of aerobic and anaerobic microorganisms.

15.6 ***Sterility Test Media Quality Controls***

15.6.1 Pre-incubation period - media should be pre-incubated to establish the sterility of the un-inoculated media. Ideally, this test should be conducted for the same length of time as the incubation time of the sterility test.

15.6.2 Fertility test - representative containers from each batch of media should be inoculated with the low numbers (< 100 cfu) of viable challenge microorganisms and incubated at the appropriate temperature to demonstrate that the media will support growth.

15.6.3 Stasis test - at the end of the incubation period for the sterility test, a number of containers should be inoculated with a small number (< 100 cfu) of challenge microorganisms. The Stasis test should be conducted approximately three (3) times a year on validated sterility test methods. If the test is not validated then the Stasis test should be conducted on each sterility test.

15.6.4 Negative controls - are samples that have been double sterilized that are put through the same manipulations as the test units.

All other administrative issuances or parts thereof, inconsistent with the provisions of this Order are hereby amended, repealed and modified accordingly.

This Order shall take effect fifteen (15) days after its publication in a newspaper of general circulation.

(Sgd) ALBERTO G. ROMUALDEZ, JR. M.D.
Secretary of Health