



No.F.6-1/2026-Lic(M-314)
Government of Pakistan
Drug Regulatory Authority of Pakistan
Division of Drug Licensing

MOST IMMEDIATE

Islamabad, the 24th February, 2026

CIRCULAR

Subject: Implementation plan of PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part-1 (PE 009-17) under S.R.O. 1587(I)/2025 dated 25-08-2025.

The Drug Regulatory Authority of Pakistan through S.R.O. 1587(I)/2025 dated 25-08-2025, has notified the transition from the existing Good Manufacturing Practice (GMP) framework prescribed under Schedule B, B-I, B-IA, B-II and B-III of the Drugs (Licensing, Registering and Advertising) Rules, 1976, to the PIC/S GMP Guide PE 009-17 (Part I) along with the relevant annexes. The notified provisions shall come into force following a six-month transition period, effective from 25th February 2026.

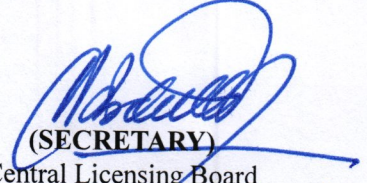
2. Keeping in view of above and in order to ensure regulatory continuity and to prevent operational disruption, a phase-wise implementation of the PIC/S GMP Guide PE 009-17 (Part I) in place of Schedule B, B-I, B-IA, B-II and B-III of the Drugs (Licensing, Registering and Advertising) Rules, 1976 was proposed in consultation with pharmaceutical stakeholders. The matter was later on placed before the Central Licensing Board in its 314th meeting, held on 23rd February, 2026, where the Board deliberated the subject matter in detail and decided as follows:

- a. Approved implementation of Chapter 4 (Documentation) of PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part-1 (PE 009-17) with effect from 25th February 2026 except Site Master File and Technical agreements which will be implemented from 1st June 2026 as mentioned in **Annex-A** of document titled "*Implementation plan of PIC/s Guide to Good Manufacturing Practice for Medicinal Products Part-1 (PE 009-17) under S.R.O. 1587(I)/2025 dated 25-08-2025.*"
- b. To ensure the smooth transition from existing schedules to PIC/S GMP Guidelines and till CLB adopts complete PIC/S GMP Guidelines; CLB has further approved Compliance Framework Documents as mentioned in **Annex-B** of the document titled "*Implementation plan of PIC/s Guide to Good Manufacturing Practice for Medicinal Products Part-1 (PE 009-17) under S.R.O. 1587(I)/2025 dated 25-08-2025*" for new entrants and pharmaceutical manufacturers holding license to manufacture by way of formulation:

Annex-B	
Compliance Framework Document-I	Requirements for establishment of a pharmaceutical unit (Premises, Equipment for production, QC, Documentation, Sanitation & Hygiene)
Compliance Framework Document-II	Requirements of Plant and Equipment
Compliance Framework Document-III	Conditions for Factory Premises
Compliance Framework Document-IV	Good Manufacturing Practices (GMPs) for License to Manufacture by Way of Formulation
Compliance Framework Document-V	Particulars to be Shown in Manufacturing Records

- c. The Board further decided to exempt Chapter No. 1 to 3 & Chapter No. 5 to 9 and remaining Annexes of PIC/S GMP Guidelines till further orders.

3. Accordingly, all pharmaceutical manufacturers are directed to comply with the above mentioned decision of the Board in letter and spirit.


(SECRETARY)
Central Licensing Board
24/02/26

Encl. Doc. Implementation plan of PIC/s Guide to Good Manufacturing Practice for Medicinal Products Part-1 (PE 009-17) under S.R.O. 1587(I)/2025 dated 25-08-2025.

Distribution:

1. Chairman, Pakistan Pharmaceutical Manufacture's Association (PPMA), Islamabad.
2. Chairman, Pharma Bureau, Karachi.
3. Pakistan Chemist and Druggist Association (PCDA), Karachi.
4. All Pakistan Pharmaceutical Manufacturers.
5. Director (QA<), DRAP, Islamabad for information and compliance.
6. Director (MIS), DRAP for uploading on DRAP's website and communication of circular to pharmaceutical manufacturers through e-app.
7. P.S. to CEO DRAP, Islamabad.

Implementation plan of PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part-1 (PE 009-17) under S.R.O. 1587(I)/2025 dated 25-08-2025.

Background:

The Drug Regulatory Authority of Pakistan (DRAP), in fulfillment of its statutory mandate under the DRAP Act, 2012 and the Drugs Act, 1976, is undertaking a strategic transition from legacy, prescriptive GMP requirements toward internationally harmonized standards based on the Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guidelines to Good Manufacturing Practices.

This transition represents a paradigm shift from rule-based, infrastructure-centric compliance toward a modern, science- and risk-based quality systems approach, consistent with practices adopted by mature regulatory authorities of world. However, national requirements governing licensing, site location, and facility design shall continue to apply. This approach ensures that regulatory modernization does not compromise public health safeguards or market stability.

Strategic objectives of PIC/S adoption:

- The strategic objectives of adopting PIC/S GMP Guidelines are to:
- Strengthen assurance of product quality, safety, and efficacy throughout the product lifecycle.
- Enhance international regulatory credibility and facilitate mutual confidence in inspections.
- Support export competitiveness of Pakistan's pharmaceutical industry.
- Promote continuous improvement, quality risk management, and pharmaceutical quality systems (PQS).
- Align national regulatory oversight with evolving global GMP expectations.

Balanced adoption approach:

CLB has adopted a balanced, phased, and risk-based approach for implementation to PIC/S GMP Guidelines as under:

Phase-I:

CLB has approved implementation of Chapter 4 (Documentation) of PIC/S Guide to Good Manufacturing Practice for Medicinal Products Part-1 (PE 009-17) with effect from 25th February 2026 except Site Master File and Technical agreements which will be implemented from 1st June 2026.

A comparative table (Table 1 & 2) on documentation requirements mentioned in old Schedules B, B-I, B-IA, B-II and B-III of the Drugs (Licensing, Registering and Advertising) Rules, 1976 with the PIC/S Chapter 4 (Documentation) has been prepared for better understanding. Most of requirements mentioned in the PIC/S Chapter 4 (Documentation) and mentioned schedules are already the same (**Annex-A**).

To ensure the smooth transition from existing schedules to PIC/S GMP Guidelines and till CLB adopts complete PIC/S GMP Guidelines; CLB has further approved Compliance Framework Documents as mentioned in **Annex-B** for new entrants and pharmaceutical manufacturers holding license to manufacture by way of formulation.

Annex-B	
Compliance Framework Document-I	Requirements for establishment of a pharmaceutical unit (Premises, Equipment for production, QC, Documentation, Sanitation & Hygiene)
Compliance Framework Document-II	Requirements of Plant and Equipment
Compliance Framework Document-III	Conditions for Factory Premises
Compliance Framework Document-IV	Good Manufacturing Practices (GMPs) for License to Manufacture by Way of Formulation
Compliance Framework Document-V	Particulars to be Shown in Manufacturing Records

CLB has further decided to exempt Chapter No. 1 to 3 & Chapter No. 5 to 9 and remaining Annexes of PIC/S GMP Guidelines till further orders.

These Compliance Framework Documents (I to V) shall be effective from 25th February, 2026. All new entrepreneurs intending to establish a pharmaceutical unit and pharmaceutical manufacturers already holding a licence to manufacture by way of formulation shall be implementing the PIC/S Chapter 4 (Documentation) of PIC/S GMP Guideline PE 009-17 (Part I) along with relevant clauses from PIC/S GMP annexes (PE 009-17 Annexes) as mentioned in **Annex-A** and the Compliance Framework Documents (I to V) (**Annex-B**) in letter and spirit.

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Annexure-A

Table 1: General Principle and Required GMP documentation (By type)

Document type (PIC/S GMP Part-1)	Equivalent / relevant Schedule section(s) of Schedule B	Current implementati on status (Under existing rules)	Applicable PIC/S Annex(es) (relevant clause/area)	Timeline
Site Master File (SMF)	None	Not Implemented	Reference: “ <i>Explanatory Notes for Pharmaceutical Manufacturers on the preparation of a Site Master File</i> ” Doc. No. PE 008-4	Effective from 01- 06-2026
Instructions (directions, or requirements) type documents:				
Specifications: Requirements with which the products or materials used or obtained during manufacture have to conform.	Schedule B: 4.2, 4.3, 4.4 Schedule B-II: 10.1.7, 10.1.8, 10.1.9, 10.2	Already Implemented	Annex 11 (specs/records in electronic form), Annex 15 (validation/spec linkage), Annex 8 (sampling vs specs), Annex 19 (retention samples vs specs)	25-02- 2026
Manufacturing formulae, processing, packaging and testing instructions	Schedule B: 4.5, 4.6, 4.8 Schedule B-II: 10.1.3, 10.3, 10.4, 10.4.5 Schedule B-III: Part I (manufacturing records particulars), Part II (records of raw materials)	Already Implemented	Annex 15 (process/cleaning validation documentation), Annex 11 (electronic batch records / e- instructions), Annex 8 (sampling instructions), Annex 19 (sample- related instructions)	25-02- 2026
Procedures (SOPs)	Schedule B: 4.7, 4.9, 4.10. Schedule B-II: 10.1.3, 10.4.6. Schedule B-III: Provides information on record templates/particula	Already Implemented	Annex 11 (SOPs for electronic systems/data integrity), Annex 15 (SOPs for validation/qualificati on) Annex 20 (risk- based procedure depth)	25-02- 2026

	rs rather than SOP system.			
Protocols: Written instructions for performing and recording operations	Schedule B: Not implemented as a defined “protocol” category though validation process is referenced Schedule B-II: 9.1	Already Implemented	Annex 15 (validation protocols/reports core expectation), Annex 11 (if protocols executed in/with computerized systems)	25-02-2026
Technical agreements: Between contract giver and acceptor for outsourced activities	Schedule B-II: supplier audits/outsourcing controls exist but not as a document type requirement.	Partially implemented	Annex 16 (release responsibility interfaces), Annex 11 (outsourced IT/service provider responsibilities), Annex 20 (risk-based oversight), plus Part I Chapter 7 (outsourcing)	Effective from 01-06-2026
Record/Report type documents				
Records: evidence of various actions taken to demonstrate compliance with instructions	Schedule B: 4.7, 4.8 Schedule B-II: 10.1.2, 10.3, 10.4, 10.4.5, 10.4.7 Schedule B-III: Part I (manufacturing record particulars), Part II (raw material records).	Already Implemented	Annex 11 (electronic records/audit trails), Annex 19 (retention/reference sample records), Annex 8 (sampling records), Annex 15 (validation records), Annex 16 (release records)	25-02-2026
Certificate of Analysis (CoA): summary of testing results on samples of products or materials against approved specifications	Schedule B-II: 10.4.5 Schedule B-III: Part I references: Analytical Report number I.A.15, I.B.15	Already Implemented	Annex 16 (release/certification relies on CoA/analytical outcome set), Annex 11 (electronic CoA/data integrity), Annex 20 (risk-based reliance on CoA and supplier CoA)	25-02-2026
Reports: Document the conduct of	Schedule B: Limited (records	Already Implemented	Annex 15 (validation reports),	25-02-2026

particular exercises, projects or investigations, together with results, conclusions and recommendations.	implied; no clear report category). Schedule B-II: 9.1, 3.4.5, 3.6, 3.7 Schedule B-III: Analytical reporting via “Analytical Report number” references (manufacturing records)		Annex 20 (risk assessments / investigation reports), Annex 11 (electronic reports/data integrity), Annex 16 (release decision reports/records), Annex 19 (stability/retention sample related reporting where used)	
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Table 2: Clause wise requirement

PIC/ S clause	Document /System/SOP required	Equivalent / relevant Schedule section(s)	Applicable PIC/S Annex(es) (relevant clause/area)	Implementation status under existing rules	Timeline
GENERATION AND CONTROL OF DOCUMENTATION					
4.1	Document Control System, Electronic Controls, Validation, Data Integrity	Schedule B Sec 4.1 (Document control). Schedule B-II Sec 10 (Documentation system).	Annex 11 – Computerized Systems: Governs electronic document control & data integrity.	Implemented	25-02-2026
4.2	Document Control	Schedule B Sec 4.1 (Preparation, review, distribution).	Annex 11: Computerized Systems: Control of document lifecycle in electronic systems.	Implemented	25-02-2026
4.3	Approval of documents	Schedule B Sec 4.1 (Approval, signature, effective date).	Annex 11: Computerized Systems: Electronic signatures & audit trails.	Implemented	25-02-2026
4.4	Formatting	Schedule B Sec 4.1 (Clarity and layout).	Annex 11: Computerized Systems: Ensures controlled templates and format validation.	Implemented	25-02-2026

4.5	Document Revision Control	Schedule B Sec 4.1 (Revision control).	Annex 11: Computerized Systems: Version control & audit trail management.	Implemented	25-02-2026
4.6	Controlled Forms	Schedule B Sec 4.1 (Controlled forms).	Annex 11: Computerized Systems: Controlled blank forms and restricted editing.	Implemented	25-02-2026
GOOD DOCUMENTATION PRACTICES					
4.7	Legibility of documents	Schedule B Sec 4.7 (SOPs & records). Schedule B-II Sec 10	Annex 11: Computerized Systems: Data integrity (ALCOA principles).	Implemented	25-02-2026
4.8	Completion and Traceability of documents	Schedule B Sec 4.7–4.8 (Contemporaneous recording). Schedule B-II Sec 10	Annex 11: Computerized Systems: Audit trail; traceability of entries.	Implemented	25-02-2026
4.9	Corrections	Schedule B Sec 4.1 (No unauthorized alteration).	Annex 11: Computerized Systems: Change history & audit trail functionality.	Implemented	25-02-2026
RETENTION OF DOCUMENTS					
4.10	Archiving	Schedule B Sec 4 (Retention).	Annex 16 – Authorized person & Batch Release: Retention for release decisions.	Implemented	25-02-2026
4.11	Retention of Batch documentation	Schedule B Sec 4.12 (Batch record retention). Schedule B-II Sec 10	Annex 16: Authorized person & Batch Release: Batch documentation required for certification.	Implemented	25-02-2026
4.12	Document retention policy	Schedule B Sec 4 Schedule B-II Sec 6	Annex 11: Computerized systems: Secure storage of electronic records. Annex 16: Authorized person & Batch	Implemented	25-02-2026

			Release: Retention supporting release traceability.		
SPECIFICATIONS					
4.13	Specifications	Schedule B Sec 4.2(iii) (Specifications). Schedule B-II Sec 6	Annex 15 – Qualification & Validation: Validation of specifications & control of changes.	Implemented	25-02-2026
4.14	Starting and packaging material Specifications	Schedule B Sec 4.3 (Starting & Packaging material specs).	Annex 8 – Sampling of Starting & Packaging Materials: Sampling plans. Annex 19 – Reference & Retention Samples: Control & storage of materials.	Implemented	25-02-2026
4.15	Intermediate and Bulk product Specifications	Schedule B Sec 4.2(iii) (Intermediate/Bulk specs). Schedule B-II Sec 6	Annex 15: Qualification and validation: Validation of in-process controls & intermediates.	Implemented	25-02-2026
4.16	Finished product Specifications	Schedule B Sec 4.4 (Finished product specs). Schedule B-II Sec 6	Annex 16: Authorized person and batch release: Final batch certification relies on approved finished specs.	Implemented	25-02-2026
MANUFACTURING FORMULA AND PROCESSING INSTRUCTIONS					
4.17	Manufacturing Formula	Schedule B Sec 4.5 (Master Formula).	Annex 15: Qualification and validation: Process validation based on master formula.	Implemented	25-02-2026
4.18	Processing Instructions, IPC, Equipment Controls,	Schedule B Sec 4.5 (Processing instructions). Schedule B-II Sec 10	Annex 15: Qualification and validation: Validated process parameters;	Implemented	25-02-2026

	Line Clearance		cleaning validation link.		
4.19	Packaging Instructions, Line Clearance	Schedule B Sec 4.6 (Packaging instructions). Schedule B-II Sec 10	Annex 15: Qualification and validation: Validation of packaging operations. Annex 16: Authorized person and batch release: Correct packaging prior to certification.	Implemented	25-02-2026
4.20	Batch Manufacturing Record	Schedule B Sec 4.12 (Batch Processing Record). Schedule B-II Sec 10 Schedule B-III (Manufacturing records)	Annex 16: Authorized person and batch release: QP/Authorized Person relies on complete BMR for release.	Implemented	25-02-2026
4.21	Batch Packaging Record	Schedule B Sec 4.12 (Batch Packaging Record). Schedule B-II Sec 10 Schedule B-III	Annex 16: Authorized person and batch release: Packaging compliance before batch certification.	Implemented	25-02-2026

PROCEDURES AND RECORD

4.22	Receipt Procedure for starting (incl. intermediate and bulk) and packaging material	Schedule B Sec 4.7(i) (Receipt SOPs). Schedule B-II Sec 7 & 10	Annex 8: Sampling of starting and packaging materials: Receipt & sampling controls.	Implemented	25-02-2026
4.23	Receipt Records	Schedule B Sec 4.7(i) (Receipt records). Schedule B-III	Annex 19: Reference and retention samples: Traceability of received materials.	Implemented	25-02-2026
4.24	Labeling, quarantine and storage of materials	Schedule B Sec 4.7(ii) (Quarantine & storage).	Annex 19: Reference and retention samples: Retention sample	Implemented	25-02-2026

		Schedule B-II Sec 10	storage conditions & segregation.		
4.25	Sampling Procedure	Schedule B Sec 4.7(iv) (Sampling SOP). Schedule B-II Sec 10	Annex 8: Sampling of starting and packaging materials: Detailed sampling requirements & prevention of contamination.	Implemented	25-02-2026
4.26	Testing Procedure	Schedule B Sec 4.8 (Testing SOPs). Schedule B-II Sec 3 & 10 Schedule B-III (Analytical format).	Annex 15: Qualification and validation: Analytical method validation. Annex 11: Computerized systems: Electronic laboratory systems (LIMS).	Implemented	25-02-2026
4.27	Release & Rejection	Schedule B Sec 4.8 (Release & rejection). Schedule B-II Sec 10 & Sec 6	Annex 16: Authorized person and batch release: Certification & release procedures.	Implemented	25-02-2026
4.28	Distribution Records	Schedule B & B-II (Distribution records).	Annex 16: Authorized person and batch release: Traceability post-certification.	Implemented	25-02-2026
4.29	QMS Documentation, Validation, Audits, Change Control, Recalls etc.	Schedule B Sec 4.7–4.10 (Validation, cleaning, complaints, change control, audits). Schedule B-II Sec 10	Annex 15: Qualification and validation: Qualification/validation documentation. Annex 11: Computerized systems: Computerized QMS systems.	Implemented	25-02-2026
4.30	Manufacturing and testing Equipment SOPs	Schedule B sec 4.7(iii) SOP for equipment Schedule B-I (Equipment requirements)	Annex 15: Qualification and validation: Equipment qualification (IQ/OQ/PQ).	Implemented	25-02-2026
4.31	Logbooks	Schedule B-I (Equipment	Annex 15: Qualification	Implemented	25-02-2026

		records/logbooks). Schedule B-II Sec 10.4.9–10.4.10	and validation: Calibration, maintenance & qualification traceability.		
4.32	Inventory of Documents	Schedule B Sec 4.1 (Controlled documentation system). Schedule B-II Sec 10 Schedule B-III	Annex 11: Computerized Systems: Master document control & version management.	Implemented	25-02-2026

**Guidance on requirements for establishment of a pharmaceutical unit
(Premises, Equipment for production, QC, Documentation, Sanitation & Hygiene)**

SECTION-I PREMISES

1. Location and Surroundings

1.1 Location: The premises shall be located preferably in an industrial area and in any case not in any residential or commercial area.

1.2 Surroundings: Premises shall be situated in an environment that, when considered together with measures to protect the manufacturing processes, presents minimum risk of causing any contamination of materials or products. It shall be away from filthy surroundings and shall not be adjacent to an open sewerage, drain, public lavatory or any factory which produces a disagreeable or obnoxious odour or fumes or large quantities of soot, dust or smoke which may contaminate the drugs being manufactured or adversely affect their quality. Existing units shall keep the surroundings under their control to be clean.

1.3 Size: The size of the plot shall not be less than 2000 square yards.

2. Building layout and its pre-approval: The building shall be of adequate size and suitable design and construction in view of the need for drugs to be manufactured and to suit the operations to be carried out. The site and layout plan of building shall be got approved from the Central licensing Board or person authorized by it in this behalf before starting construction of the building and any minor subsequent changes in the layout plan will be communicated as and when made with a revised updated layout plan at the time of renewal of Drug Manufacturing Licence.

3. Building design and construction (General)

3.1 General: The layout and design shall aim at minimizing the risk of errors, facilitate good sanitation and permit effective clearing and maintenance in order to avoid cross contamination, build-up of dust or dirt, and, in general, any adverse affect on the quality of products.

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

3.3. Protection against insects: Premises shall be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

3.4 Surfaces: In areas where raw materials, in-process materials or drugs are exposed, the following general condition shall apply to the extent necessary to prevent contamination, namely:-

- (i) floors, walls, and ceilings permit easy cleaning, brick, cement blocks, and other porous materials are sealed;
- (ii) floors, walls, ceilings, and other surfaces are hard, smooth, and free of sharp corners where extraneous material can collect;
- (iii) joints are sealed between walls, ceilings and floors;
- (iv) pipes, light fittings, ventilation points and other services do not create surfaces that cannot be cleaned; and
- (v) screened and trapped floor drains are provided if required.

4. Storage areas

4.1 Capacity: Storage area shall be properly defined of sufficient capacity to allow orderly storage of various categories of materials and products: starting and packaging materials, intermediates bulk and finished products, products in quarantine, and, released, rejected, returned, or recalled products.

4.2. Design: Storage areas shall be designed or adapted to ensure good storage conditions. In particular, they shall be clean and dry, suitably lit and maintained within acceptable temperature limits which should be commensurate with storage requirements of the drugs. Where special storage conditions are required (e.g., controlled temperature and humidity) these shall be provided, checked, and monitored.

4.3 Bays: Receiving and dispatch bays shall protect materials and products from the weather, reception areas shall be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

4.4. Quarantine: Well defined quarantine areas shall be provided for the incoming materials, in process materials and finished drugs. Where quarantine status is ensured by storage in separate areas; these areas shall be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine shall be given equivalent security.

4.5 Sampling: There shall normally be a separate sampling area for starting materials. If sampling is to be performed in the storage area, it shall be provided in such a way as to prevent contamination or cross-contamination.

4.6. Rejected Materials: Segregation in a separate area shall be provided for the storage of rejected, recalled, or returned materials or products.

4.7. Special Materials: Highly active materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire, or explosion shall be stored in safe and secure areas.

4.8. Packaging Materials: Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labelling, and special attention shall be paid to the safe and secure storage of these materials.

4.9. Weighing Area: The weighing of starting materials on the basis of estimation of yield shall be carried out in separate weighing areas designed for that use with provisions for dust control. Separate provisions shall be made for materials posing high risks of contamination, like steroids and antibiotics especially penicillin.

5. Production Department

5.1. General Facilities: A Production Department shall be provided which shall have all necessary facilities including:-

- (i) Adequate number of appropriately qualified and trained technical personnel;
- (ii) Adequate and properly planned areas;
- (iii) Suitable equipment, instruments and containers for manufacture including their validation where necessary;
- (iv) Clearly defined manufacturing processes shown to be capable of consistently manufacturing pharmaceutical products of the required quality and complying with their specifications;
- (v) Validated critical steps of manufacturing processes;
- (vi) Procedures and instructions; for working approved by the Quality Control Department;
- (vii) Suitable storage places for in-process materials;
- (viii) Adequate number of technically trained and skilled personnel and equipment for in-process controls;
- (ix) Skilled operators trained to carry out procedure's correctly, the record of training should be available; and
- (x) Appropriate air handling system to avoid contamination and cross contamination.

5.2. Dedicated facilities for production

Dedicated and self-contained facilities for the production of particular drugs shall be provided in addition to the general facilities such as highly sensitizing materials (e.g., penicillin) or biological preparations (e.g., live microorganisms) or cytotoxic substances or radiopharmaceutical or veterinary immunological preparations or sterile products or for that matter such other highly active pharmaceutical products, antibiotics, hormones as may be identified by the Central Licensing Board at any stage in order to minimize the risk of a serious medical hazard due to cross-contamination. Veterinary products containing ingredients similar to those used for human health and of the same quality can be manufactured in the same premises used for manufacture of pharmaceutical. Products, however, simultaneously human drugs shall not be manufactured. Non-pharmaceutical products, technical positions, such as pesticides shall not be manufactured in the same premises already used for the manufacture of pharmaceutical products. In exceptional cases of emergency, the principle of campaign working in the same facilities may be allowed by the Central Licensing Board provided that specific precautions are taken and the necessary validations are made.

5.3 General requirement for production areas

- (i) Layout: the production area shall preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
- (ii) Adequacy: The adequacy of the working and in-process storage space shall permit the orderly and logical placement of equipment and materials so as to minimize, the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission, error or wrong application of any of the manufacturing or control steps.
- (iii) Surfaces: Starting and primary packaging; materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors* and ceilings) shall be smooth and free from cracks and open joints shall not shed particulate matter, and shall permit easy and effective clearing and, if necessary, disinfection.
- (iv) Services: Pipework, light fittings, ventilation points and other services shall be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they shall be accessible from outside the manufacturing areas.
- (v) Drains: Drains shall be of adequate size and equipped to prevent backflow. Open channels shall be avoided.
- (vi) Environmental Controls: Production areas shall be effectively ventilated, with air-control facilities (including control of temperature and, where necessary, humidity and filtration) appropriate to the products handled to the operations undertaken, and to the external environment. These areas shall be regularly monitored during production and non-production periods to ensure compliance with their design specifications.
- (vii) Packaging: Area(s) for the packaging of pharmaceutical products shall be specifically designed and laid out so as to avoid mix-ups or cross contamination.
- (viii) Light: Production areas shall be well lit, particularly where visual online controls are carried out.

6. Ancillary areas

6.1 Rest rooms: Rest and refreshment rooms shall be separate from other areas.

6.2 Changing rooms: Facilities shall be provided for changing and storing clothes and for washing and toilet purposes: which shall be easily accessible and appropriate for the number of users. Toilets shall not communicate directly with product or storage areas.

6.3 Workshops: Maintenance workshops shall preferably be separated from production areas. Whenever parts and tools are stored in the production area, they shall be kept in rooms or lockers reserved for that use.

6.4 Animal House: Animal houses shall be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

SECTION-2

EQUIPMENT FOR PRODUCTION

2.1. General: The all necessary equipment shall be provided which shall be so designed constructed, located, installed and maintained as to suit the operations to be carried out, and the layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

2.2. Layout: The equipment shall be so laid that:--

- (a) permits it function in accordance with its intended use. Parts in contact with raw materials in-process materials, or drugs are accessible to cleaning or are removable;
- (b) permits cleaning of adjacent areas and does not interfere with other processing operations, and in also minimizes circulation of personnel and optimizes flow of material;
- (c) prevents the contamination of drugs by other drugs, by dust, and by foreign material such as rust, lubricant, and particles coming from the equipment; and
- (d) the base of immovable equipment is adequately sealed along points of contract with the floor.

2.3: Construction: The equipment shall, be so constructed that it does not add extraneous material to the drug and for that:-

- (a) the surfaces that come in contract with raw materials, in-process materials, or drugs are smooth and, are made of materials that is non-toxic, corrosion resistant, non-reactive to the drug being manufactured, and capable of withstanding repeated cleaning or sanitizing;
- (b) the design is such that the possibility of a lubricant or other maintenance material contaminating the drug is minimum;
- (c) wooden equipment and equipment made of material that is prone to shed particles or to harbour bacteria do not come in contact or contaminate raw materials, inprocess materials, or drugs; and
- (d) chain drives and transmission gears are enclosed or properly covered.

2.4. Piping. All service piping and devices shall be clearly labeled to indicate the contents and, where applicable, the direction of flow, and special attentions be paid to the provision of non-interchangeable connections or adopters for dangerous gases and liquids.

2.5. Tanks: Tanks used in processing liquids and ointments are equipped with fitting that can be dismantled and cleaned and are provided with appropriate covers.

2.6. Filters: Filter assemblies are designed for easy dismantling.

2.7. Cleaning equipment: Washing and cleaning equipment shall be provided which shall not be a source of contamination.

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

SECTION-3

QUALITY CONTROL DEPARTMENT

3.1. General: The Quality Control Department shall be independent with adequate number of trained personnel and under the authority of a person who shall be a full time employee.

3.2. laboratories: Adequate laboratory facilities shall be provided with necessary equipment and instrument, glassware, chemicals, reagents etc. suited to testing procedures of drugs to be manufactured.

3.3. Area: the quality control laboratories shall have adequate areas which shall:--

- (i) be separated from production areas, and the areas where biological, microbiological or radioisotope test methods are employed shall be separated from each other;
- (ii) be designed to suit the operations to be carried out in them and sufficient space shall be given to avoid mix-ups and cross-contaminations;
- (iii) be so designed so that it takes into account the suitability of construction materials, fume prevention and ventilation and separate air handling units and other requirements shall be provided for biological, microbiological, sterility testing and radioisotope laboratories;
- (iv) have separate room for highly sensitive instruments to protect these against electrical interference, vibrations, contact with excessive moisture and other external factors or where there is need to isolate the instrument; and
- (v) have appropriate facilities to store samples and records.

3.4 Facilities: The quality control laboratory shall have:

- (i) satisfactory equipment required for test and analysis of drugs intended to be manufactured, protocols for test and analysis of drugs to be manufactured including their validation where necessary;
- (ii) have adequate other facilities and approved procedures for sampling inspecting and testing starting materials, packaging, materials, intermediate, bulk, and finished, products and where applicable for monitoring environmental conditions for good manufacturing practice purposes;
- (iii) written procedures specifically:--
 - a. validation of methods of manufacture and quality control testing;
 - b. validation of equipment and instruments and cleaning procedures;
 - c. stability testing of the active pharmaceutical substances and the finished drugs; and
 - d. determining the shelf life of both raw materials and finished drugs.
- (iv) Validation studies conducted for important equipment or instruments, methods of manufacture and quality control and cleaning procedures in accordance with predefined protocols. A written report summarizing results and conclusions shall be available.
- (v) Separate facilities for the bulk storage of volatile and inflammable materials.

SECTION-4
DOCUMENTATION

4.1 General the documents shall:

- (i) Be designed and prepared, complying with the relevant parts of the drug registration approvals;
- (ii) Be approved, signed, and dated by appropriate authorized persons and shall not be changed without authorization;
- (iii) Have unambiguous contents and shall clearly state the title, nature, and purpose, and they shall be laid out in an orderly fashion and be easy to check, reproduced documents shall clear and legible.

4.2. Specifications and Testing Procedures: Following documents shall be available: -

- (i) Reference Bodies: Pharmacopoeias, reference standards, reference spectra, and other reference materials, where necessary;
- (ii) Testing Procedures: Validated testing procedures in the context of available facilities and equipment;
- (iii) Specifications: Appropriately authorized and dated specifications, including tests on identity, content, purity, and quality, for starting and packaging materials and finished products; and where appropriate, for intermediate or bulk products. Specifications for water, solvents, and reagents (e.g., acids and gases) used in production shall also be included.

4.3 Specification for Starting and Packaging Materials: Specifications for starting and primary or prihted packaging materials shall include, if applicable:--

- (i) The designated name (if applicable, the International Non-proprietary Name) and internal code reference;
- (ii) The reference, if any, to a pharmacopoeial monograph;
- (iii) Qualitative and quantitative requirements with acceptance limits; and
- (iv) Packaging material shall conform to specifications, with emphasis placed on the compatibility of the material with the drug product it contains.

4.4. Specifications for Finished Products: Specification for finished products shall include:-

- (i) the designated name of the product and the code reference where applicable;
- (ii) the designated name (s) of the active ingredient (s) if applicable, the International Non-proprietary Name);
- (iii) the label claim or the reference to the formula;
- (iv) a description of the dosage form;
- (v) direction for sampling and testing or a reference to procedures;
- (vi) the qualitative and quantitative requirements with acceptance limits;
- (vii) the storage conditions and precautions where applicable; and (viii) the shelf-life.

4.5. Master formula: A formally authorized master formula shall exist for each product and: batch size to be manufactured, which shall include:

- (i) the name of the product, with a product reference code relating to its specifications;
- (ii) a description of the dosage form, strength of the product, and batch size;
- (iii) a list of all starting materials to be used (if applicable, with the International non-proprietary Name), with the amount of each described, using the designated name and a reference that is unique to that material (mention shall be made of any substance that may disappear in the course of processing) and a reference number or code number to its quality control testing;
- (iv) a statement of the expected final yield with the acceptance limits, and relevant intermediate yields where applicable;
- (v) a statement of the processing location and the principal equipment to be used;
- (vi) detailed step-wise processing instructions (e.g., checks on materials, pretreatment, sequence for adding materials, mixing times, temperatures);
- (vii) the instructions for any in-process controls with their limits;
- (viii) where necessary, the requirements for storage of the products, including the container, the labelling and any special storage conditions; and
- (ix) any special precautions to be observed.

4.6. Packaging instruction: Formally authorized packaging instructions shall exist for each product, pack size, and type which shall normally include or made reference to:-- (i) the name of the product;

- (ii) a description of its pharmaceutical form, strength and method of application where applicable;
- (iii) the pack size expressed in terms of the number, weight, or volume of the product in the final container;
- (iv) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications for each packaging materials;
- (v) where appropriate an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry ate of the product have been marked;
- (vi) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before operations begin;
- (vii) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used; and
- (viii) details of in-process controls with instructions for sampling and acceptance limits.

4.7. Standard Operating Procedures and Records: There shall be standard operating procedures for:--

- (i) the receipt of each delivery of starting material and primary and printed packaging material;
- (ii) the internal labelling, quarantine, and storage of starting materials, packaging materials, and other materials as appropriate;

- (iii) each instrument and piece of equipment. These shall be placed in close proximity to the equipment;
- (iv) sampling, which specify the person (s) authorized to take samples, and the sampling instructions shall include:--
 - (a) the method of sampling and the sampling plan;
 - (b) the equipment to be used;
 - (c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
 - (d) the amount of sample to be taken;;
 - (e) instructions for any required sub-division of the samples;
 - (f) the type of sample container to be used, and whether they are for aseptic sampling or for normal sampling; and
 - (g) any specific precautions to be observed, especially in regard to the sampling of sterile or naxious material;
- (v) Describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk, or finished product is identified with a specific batch number;
- (vi) For batch numbering that are applied to the processing stage and to the respective packaging stage shall be related to each other;
- (vii) For batch numbering shall assure that the same batch numbers will not be repeatedly used; this applies also to reprocessing.

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

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

4.9. There shall be written procedures, assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used and facilities to be cleared and such written procedures shall be followed.

4.10. Written standard operating procedures and the associated records of actions taken shall be available, for:-

- (a) equipment assembly and validation;
- (b) analytical apparatus and cilbration;
- (c) maintenance, cleaning and sanitization;
- (d) personnel matters including qualifications, training, clothing, hygiene;
- (e) environmental monitoring;
- (f) pest control;

- (g) complaints;
- (h) recalls;
- (i) returns;

4.11. Labels.

4.11.1. Labels firmly affixed or security attached to containers, equipment or working areas shall be clear and unambiguous and shall indicate the status like “quarantined” “accepted” “rejected” “clean”, etc.

4.11.2. All finished drugs shall be labelled in accordance with the approval of Registration Board and with at least the following information:-

- (a) the name of the drug;
- (b) a list of the active ingredients, showing the amount of each present, and a statement of the net contents, e.g., number of dosage units, weight or volume;
- (c) the batch number assigned by the manufacturer;
- (d) the expiry date;
- (e) any special storage conditions or handling precautions that may be necessary;
- (f) direction for use, and warnings and precautions that may be necessary; and
- (g) the name and address of the manufacturer or the Company or the person responsible for placing the drug on the market.

4.11.3. The label or accompanying document of reference standards shall indicate concentrations, date of manufacture, expiry date, date the closure is first opened and storage conditions where appropriate.

4.12. Batch Processing Records.

4.12.1. A Batch Processing Record shall be maintained for each batch processed. It shall be based on the relevant portions of the approved Master Formula and Processing Instructions.

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

4.12.3. During processing the following information shall be recorded and, after completion, the record shall be dated and signed in agreement by the person responsible for the processing operation:

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

SECTION-5

SANITATION AND HYGIENE

5.1: Sanitation: A written sanitation programme shall be available which will include instructions on the sanitary production of drugs and the handling of materials used in the production of drugs, and, in particular, indicating the following cleaning procedures for the premises and the equipment used in the production of the drug, namely:--

- (i) cleaning requirements applicable to all production areas of the plant, with emphasis on manufacturing areas that require special attention;
- (ii) cleaning requirements applicable to processing equipment;
- (iii) cleaning intervals;
- (iv) cleaning materials, their concentration, and the equipment to be used;
- (v) responsibilities of outside contractors, if any;
- (vi) disposal procedures for waste material and debris;
- (vii) pest control measures;
- (viii) precautions required to prevent contamination of a drug when rodenticides, insecticides, and fumigation agents are used;
- (ix) microbial and environmental monitoring procedures and limits in areas where susceptible products are manufactured; and
- (x) the personnel responsible for carrying out cleaning procedures.

5.2. Hygiene

5.2.1. Minimum requirements of health, hygienic behavior and clothing for personnel shall be available in writing in order to ensure the clean and sanitary production of the drug.

5.2.2. No person who is affected with or is a carrier of a disease in a communicable form, or has an open lesion on any exposed surface of the body shall be employed for areas where a drug during any stage of its production is exposed.

5.2.3. Minimum requirements of health shall be available in writing and shall provide for:--

- (i) pre-employment medical examination;
- (ii) assessment of an employee's health prior to return to his place of employment following illness involving a communicable disease;
- (iii) action to be taken in the event of a positive diagnosis or a case suspected of being hazardous to consumers of the products; and
- (iv) Routine supervisory check system of employees.

5.2.4. The hygiene programme shall clearly define clothing requirements and hygiene procedures for company personnel and visitors including the following:--

- (i) Where a potential for the contamination of a raw materials, in-process material, or drug exists, individuals shall wear clean clothing and protective covering;
- (ii) Eating, smoking, or any unhygienic practice shall not be permitted in production areas;
- (iii) Requirements concerning personal hygiene, with emphasis on hand hygiene;
- (iv) Requirements concerning cosmetics and jewellery worn by employees.]

Guidance on Requirements of Plant and Equipment

(A) The Following equipment is required for the manufacture of drugs for external appliances or suspension:--

(1) Mixing tanks where applicable.

(2) Kettles, steam, gas or electrically heated.

(3) A suitable power driven mixer.

(4) Storage tanks or pots.

(5) A colloid mill or a suitable emulsifier or homogeniser, where applicable.

(6) A trip-roller mill or an ointment mill, where applicable.

(7) Liquid filling equipment.

(8) Jar or tube filling equipment, where applicable.

Area of minimum of 200 square feet is required for the basic installation.

(B) The following equipment is required for manufacture of Syrups, Exlixirs and Solution:--

(1) Mixing and storage tanks.

(2) Mixer.

(3) Filter press or other suitable filtering equipment such as metal filter or sparkled filter or Also –pad filter.

(4) Water still or Deioniser.

(5) Various liquid measures and weighing scale.

An area of maximum 300 square feet is required for the basic installations.

(C) Equipment for the manufacture of Pills and Compressed Tablets including Hypodermic Tablets. For efficient operation, the tablet production department shall be divided into the following three distinct and separate section situated in different rooms:

- 1 Granulating Section;
- 2 Tableting Section;
- 3 Coating Section. ♦

The following equipment is required in each of the three section:-

1. Granulating Section. (1) Disintegrator, where applicable.

(2) Power mixer granulation mixer with stainless steel cabinet parts.

(3) Granulator.

(4) Oven thermostatically controlled.

Tableting Section:--

(1) Tablet machine, single punch or rotary.

- (2) Pill machine, where applicable.
- (3) Punch and dyes storages cabinet.

The Tableting Section shall be free from dust and floating particles. For this purpose, it is desirable that each tablet machine is connected either to an exhaust system or isolated into cubicles.

Coating Section:--

- (1) Jacketed kettle, or equivalent steam, gas or directly heated for preparing solution.
- (2) Coating pan.
- (3) Polishing pan, where applicable.
- (4) Heater and exhaust system, where applicable.

The coating section shall be made dust-free and suitable exhaust provided to remove excess powder and the fumes resulting from solvent evaporation.

A total area of not less than 900 square feet for the three Sections is required for basic installations.

The manufacture of Hypodermic Tablets shall be conducted under aseptic conditions in a separate air-conditioned room, the walls of which shall be smooth and washable. The granulations, tableting and packing shall be done in this room.

(D) The following equipment is required for the manufacture of powders:-

- (1) Disintegrator, where applicable.
- (2) Mixer
- (3) Sifter or sieve.
- (4) Stainless steel vessels and scoops of suitable material.
- (5) Filling equipment.

In the case of operations involving floating particles of fine powder or dust a suitable exhaust system shall be provided. Workers shall be provided with suitable marks during operation.

If a manufacturer has a tablet section where the power of the granules can be manufactured: provided that such granules or powder or non-toxic, no separate equipment will be required for manufacture of such powder as granules.

(E) The following equipment is required for filing of Hard Gelatin Capsules:--

- (1) Mixing and blending equipment.
- (2) Capsules filling units.

An area of minimum of 200 square feet is required for the basic installations. The room shall be air-conditioned and also dehumidified wherever necessary.

(F) The following equipment is required for the manufacture of Surgical Dressings other than Absorbent Cotton Wool:--

- (1) Rolling machine.

- (2) Trimming machine.
- (3) Cutting equipment.
- (4) Folding and pressing machine for gauze.
- (5) Mixing tanks for processing medicated dressings.
- (6) Hot air drying ovens.
- (7) Steam sterilizer or dry heat sterilizer.

An area of minimum of 300 square feet is required for the basic installations. In case medicated dressings are to be manufactured, room with an area of minimum of 300 square feet shall be provided.

(G) The following equipment is required for the manufacture under aseptic conditions of Eye-Ointments, Eye-Drops, Eye-Lotions and other use:-

- (1) Hot air oven electricity heated with thermostatic control.
- (2) Kettle, gas or electrically heated with suitable mixing arrangement.
- (3) Colloid mill or homogeniser.
- (4) Tube filling equipment.
- (5) Mixing and storage tanks of stainless steel or of other suitable materials.
- (6) Sintered glass funnel, seitz filter or filter candle.
- (7) Liquid filling equipment.
- (8) Autoclave.

An area of minimum of 250 square feet is required for the basic installation. The manufacture and filling shall be carried out in an air-conditioned room under aseptic conditions. The room shall be further dehumidified if preparations containing antibiotics are manufactured.

(H) The following equipment is required for the manufacture of Pessaries and Suppositories:

- (1) Mixing and pouring equipment.
- (2) Moulding equipment.

An area of minimum of 200 square feet required for the basic installation.

In case of pessaries manufactured by granulation compression, if the licence does not have a tablet section, a separate area of minimum of 300 square feet and the following equipment is necessary:-

- (1) Mixer.
- (2) Granulator.
- (3) Drier.
- (4) Compressing machine.

(5) Pessary and tablet counter.

(J) The following equipment is required for the manufacture of inhalers and Vitallae:

- (1) Mixing equipment.
- (2) Graduated delivery equipment for measurement of the medicament.
- (3) Sealing equipment.

An area of minimum of 200 square feet is required for basic installations.

(J) The following equipment is required for the repacking installations of drugs and Pharmaceutical Chemicals:--

- (1) Sifter.
- (2) Stainless steel scops and vessels.
- (3) Weighing and measuring equipment.
- (4) Filling equipment.

An area of minimum of 300 square feet is required for basic packing operations. In the case of operations invoking floating particles of fine powder or dust, a suitable exhaust system should be provided.

(K) Requirements for the manufacture of parenteral preparations:-- The whole process of the manufacture of parenteral preparations may be divided into the following separate operations:--

- (a) Preparation of the container.—This includes, cutting, washing, drying sterilization of ampoules or vials prior to filling.
- (b) Preparation of solution.-- This includes preparation and filtration of solution.
- (c) Filling and sealing.--This includes filling and sealing of ampoules or filling and capping of vials.
- (d) Sterilization.
- (e) Testing.

The following basic hygienic requirements shall be complied with:--

- (1) Strict sanitation shall be maintained throughout the entire plant in order to prevent contamination and to keep out pyrogens. Masks and overalls shall be worn wherever necessary.
- (2) The preparation room where the solutions are prepared shall be of such a nature that may be kept scrupulously clean. This room shall be air-conditioned.
- (3) The filling and sealing rooms shall likewise be air-conditioned under positive pressure with air locks provided to prevent the entry of air from outside. The walls and floors shall be such as may permit their being sprayed and washed with an antiseptic solution. The benches shall preferably have stainless steel or laminated plastic tops capable of being washed.
- (4) In the room provided for aseptic filling and sealing, necessary measures for maintaining sterility and to preventing contamination shall be adopted.
- (5) A separate room shall be provided for sterilization, testing (for leaks and floating particles) and drying.
- (6) finished products shall be stored in a suitable separate place.

The following equipment required:

Manufacturing Area:--

- (1) Storage equipment for ampoules and vials.
- (2) Ampoule washing and drying equipment.
- (3) Dust proof storage cabinets.

- (4) Water still.
- (5) Mixing and preparation tanks or other containers. The tanks or containers shall be made of either glass or such material which will not react with the liquid.
- (6) Filtering equipments such as filter pass or sintered glass funnel.
- (7) Autoclave.
- (8) Hot Air Steriliser.

Filling and sealing room:--

- (9) Benches for filling and sealing.
- (10) Filling and sealing unit.

Aseptic filling and sealing room:--

- (11) Bacteriological filters such as seitz filter, candles or sintered glass filters.
- (12) Filling sealing unit. General Room:--
- (13) Inspection table with draft and light background.
- (14) Leak testing equipment. ♦
- (15) Labelling and packing benches.
- (16) Storage equipment including cold storage and refrigerators, if necessary.

Note I. The above requirements of this guidance document are subject to modifications at the discretion of the Central Licensing board if it is of the opinion that having regard to the nature and extent of the manufacturing operations it is necessary to relax or alter in the circumstances of a particular case:

Provided that such variation shall be recorded in writing with reasons therefore and also communicated in writing to the manufacture for his record.

Note II. This guidance document gives equipment and space required for certain categories of drugs only. There are, in addition, other categories such as drugs miscellaneous pharmaceuticals such as Ferries Ammoni Citras, Potassium Citras, Glycerin, Paraffin, Oxygen gas, Disinfectant fluids, mechanical contraceptives, surgical cotton and tinctures which are not listed in this guidance document. The Central Licensing Board shall, in respect of such categories of drugs, have the discretion to examine the adequacy or otherwise of factory premises, space, plant, machinery and other requirements having regard to the nature and extent of the manufacture to carry out necessary modifications in them and, on the modification having been made, approve of the manufacture of such categories of drugs. Any drug so permitted to be manufactured by the Central Licensing Board shall be deemed to be an additional category of drug for the purpose of this guidance document.

Guidance on Conditions for Factory Premises

CONDITIONS OF FACTORY PREMISES

(for registration of insecticides, pesticides and household disinfectants)

1. Location and surrounding.--The premises should be away from drinking water sources and are liable to flooding.

2. (a) Building.-- Building should be provided with both good general ventilation and protection against direct sunlight, with easy access for fire-fighting equipment including fire extinguishers, fire blankets, hose, reels and fire-alarm etc. Sufficient water must be available for fire-fighting.

(b) Walls.--Walls as far as possible should be protected by non-flammable or slow burning material.

(c) Doors.--Doors must be fire resistant preferably with self-closing system.

(d) Floors.--Floor should be impermeable to liquids, smooth and free from cracks. There should be no drains at all in plants and in warehouse. If drains are absolutely necessary they must not connect directly with waterways or public sewers.

(e) Signs.--Signs indicating smoking restrictions, location of emergency kits, firefighting equipment, telephone and escape routes must be prominently displayed. Local exhaust system must be effective.

3. Personnel.--The avoidance of intoxication by skin contact, inhalation of fumes. Vapours and dust, accidental ingestion, the protection of clothing and equipment, e.g. protective helmet or cloth cap, eye protection (safety spectacles, goggles or face shield) dust or light fume mask, one piece work suit with closely fitting trouser bottoms, rubber or plastic gloves or gauntlets, rubber or plastic apron, and work boots with protective toecaps, must be provided.

Staff must not be allowed to go home wearing the same clothing they wore at work; emergency showers and eye washing facilities must be provided in the premises. Safety instructions should be strategically displayed in local language. All emergency and safety equipment must be frequently and regularly checked and maintained to ensure its conditions satisfactory.

4. Medical Services.--There must be pre-employment medical examination for all staff members whether working permanently or on contract basis. When organophosphates or carbamates are handled pre-exposure baseline blood cholinesterase level must be determined for all operational staff. Staff regularly engaged in formulation and packing procedures and maintenances must have their cholinesterase levels checked regularly and detailed records must be kept. The check should be carried out by a properly equipped hospital or laboratory under qualified expert.

“Levels of cholinesterase activity should be interpreted by a doctor, but the following guide might be helpful:--

(i) A decrease of more than 20% in blood cholinesterase activity from the preexposure value indicates that the cause should be investigated.

(ii) A decrease of more than 40% in blood cholinesterase activity from the preexposure value indicates that the worker concerned should be removed from further exposure to organophosphates or carbamates.

Workers should not be exposed again to cholinesterase inhibiting compounds until further tests show a blood cholinesterase activity within 20% of the pre-exposure value.

**Guidance on Good Manufacturing Practices (GMPs) for License to Manufacture
by Way of Formulation**

**PART-I
GENERAL CONDITIONS
SECTION-I**

1. Responsibility of licensee for drug's fitness of use

The licensee shall assume the responsibility for the quality of the drugs manufactured by it to ensure that they are fit for their intended use, comply with the requirements of the Ordinance and rules made thereunder and do not place patients at risk due to inadequate safety, quality or efficacy. To achieve the quality objective reliably, there shall be a comprehensively designed and correctly implemented system of quality assurance incorporating good manufacturing practices and quality control. It shall be fully documented and its effectiveness monitored. All part of the quality assurance system shall be adequately staffed with competent personnel, and shall have suitable and sufficient premises, equipment, and facilities.

SECTION-2

2. Quality assurance system

The licensee shall have a system of quality assurance appropriate to the manufacture of drugs which shall ensure that:--

- (a) drugs are designed and developed in a way that takes into account the requirements of good manufacturing practices and other associated codes as may be notified from time to time;
- (b) production and control operations are clearly specified in a written form and good manufacturing practices requirements are adopted and followed;
- (c) managerial responsibilities are clearly specified in job descriptions;
- (d) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;
- (e) all necessary controls on starting materials, intermediate products, and bulk products and other in process controls, calibrations and validations are carried out;
- (f) the finished products are correctly processed and checked, according to the defined procedures;
- (g) finished drugs are not sold or supplied before the authorized person (s) has certified that each production batch has been produced and controlled in accordance with the requirements of the good manufacturing practices and the relevant rules made under the Ordinance relevant to the production, control and release of drugs as well as of conditions of registration;
- (h) satisfactory arrangements exist to store in appropriate storage conditions;
- (i) there is a procedure for self-inspection and or quality audit at appropriate intervals that regularly reviews the effectiveness and applicability of the quality assurance system and that such a procedure is followed; and
- (j) a system exist in the form of written Standard Operating Procedure according to which complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measure taken in respect of the defective products and to prevent recurrence and that system is followed.

SECTION-3

3. Quality Control

3.1 Quality control department: The licensee shall maintain and satisfactory run its quality control department which is independent of other departments and under the authority of a person with the required qualifications and experience and with adequate facilities to ensure that all the quality control arrangements are effectively and reliably carried out.

3.2 Basic requirements: The basic requirements to be met for quality control shall be as follows: --

- (a) during the period of validity of licence, adequate facilities, trained personnel and approved procedures are available for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for good manufacturing practices purposes.
- (b) samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by methods and personnel approved of by the quality control department;
- (c) test methods are validated;
- (d) records are made manually and or by recording instruments demonstrating that all the required sampling, inspecting, and testing procedures have actually been carried out and that any deviation has been fully recorded and investigated;
- (e) the finished products contain ingredients complying with the qualitative and quantitative composition of the products described in the marketing authorization, the ingredients shall be of the required purity, in their proper container, and correctly labelled;
- (f) records are made of the results of inspecting and testing materials and intermediate, bulk, and finished products against specifications and product assessment includes a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;
- (g) no batch of product is released for sale prior to certification by the authorised persons(s) that it is in accordance with the requirements of the rules;
- (h) sufficient samples of starting materials and products are retained to permit future examination of the product if necessary and the retained product is kept in its final pack unless the pack is exceptionally large; and
- (i) all quality control procedures are established, validated and implemented; the reference standards for substances are evaluated, maintained, and stored; correct labelling of containers of materials and products is ensured; the stability of the active pharmaceutical ingredients and products is monitored; complaints related to the quality of the product are investigated and environmental monitoring is conducted. All these operations shall be carried out in accordance with written procedures and where necessary, recorded, provided that the Central Licensing Board may allow other arrangements if it is considered necessary for an effective quality control system of the licensee.

3.3 Control Procedures:

3.3.1 General: All tests and analysis conducted shall be in accordance with the instructions given in the relevant written test procedures. The result shall be checked by the supervisor before the materials or product is released or rejected.

3.3.2 Sampling: The samples shall: --

- (a) be representative of the batches of material from which they are taken and in accordance with the approved written procedure;
- (b) be taken in a manner so as to avoid contamination or other adverse effects on quality, and the containers that have been sampled shall be marked accordingly and carefully resealed after sampling;
- (c) be taken with care to guard against contamination or mix-up of or by the material being sampled, all sampling equipment that comes into contact with the material shall be clean, and some particularly hazardous or potent materials may require special precautions;
- (d) be taken with equipment which shall be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment; and
- (e) bear a label indicating: --
 - (i) the name of the sampled material;
 - (ii) the batch or lot number;
 - (iii) identify the container from which the sample has been taken;
 - (iv) the signature of the person who has taken the sample;
 - and (v) the date of sampling.

3.3.3 Test requirement for starting and packaging materials:

- (i) Test before use: Before releasing a starting or packaging material for use, the quality control manager shall ensure that the materials have been tested for conformity with specifications for identity, strength, purity, and other quality parameters.
- (ii) Identity from each container: An identity test shall be conducted on a sample from each container of starting materials.
- (iii) Examination of each batch: each batch (lot) of printed packaging materials shall be examined following receipt.

3.3.4 Test requirement for in-process control:

Records of testing: In-process control records shall be maintained and form a part of the batch records.

3.3.5 Test requirements for furnished products:

- (i) Testing each batch: For each batch of drug product, there shall be an appropriate laboratory determination of satisfactory conformity to its finished product specifications prior to release.
- (ii) Rejection of failed products: Product failing to meet the established specifications or any other relevant quality criteria may be revalidated and shall be rejected if they do not qualify revalidation protocols.
- (iii) Reprocessing: Reprocessing may be performed, if feasible, but the reprocessed product shall meet all specifications and other quality criteria prior to its acceptance and release.

3.3.6 Production record and batch review:

- (i) Review of Records: Production and control records shall be reviewed and any divergence or failure of a batch to meet its specifications shall be thoroughly

investigated, the investigation shall, if necessary, extend, to other batches of the same product and extend, to other batches of the same product and other products that may have been associated with the specific failure or discrepancy, and a written record of the investigation shall be made and shall include the conclusion and details of follow-up action.

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

3.3.7 Stability studies:

- (i) The quality control department shall:--
 - (a) evaluate the quality and stability of finished pharmaceutical products and, of starting materials and intermediate products; and
 - (b) establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.
- (ii) A written programme for ongoing stability determination shall be developed and implemented to include elements such as: --
 - (a) a complete description of the drug involved in the study;
 - (b) the complete testing parameters and methods describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
 - (c) provision for the inclusion of a sufficient number of batches;
 - (d) the testing schedule for each drug;
 - (e) provision for special storage conditions;
 - (f) provision for adequate sample retention; and
 - (g) a summary of all the data generated, including the evaluation and the conclusions of the study.
- (iii) Stability of the finished product shall be evaluated and documented prior to marketing and following any significant changes in the processes, equipment, primary packaging materials, etc.

3.4. Self-inspection:

3.4.1. General: The licensee shall conduct repeated self-inspection with a view to evaluate its own compliance with good manufacturing practices in all aspects of production and quality control. The self-inspection programme shall be designed to detect any shortcomings in the implementation of good manufacturing practices and to recommend the necessary corrective actions; Self-inspections shall be performed routinely, and may be, in addition,

performed on special occasions, e.g., in the case of product recalls or repeated rejections or when an inspection by the Central Licensing Board is required. The team responsible for self-inspection shall consist of personnel who can evaluate the implementation of good manufacturing practices objectively; all recommendations for corrective action shall be implemented. The procedure for self-inspection shall be documented, and there shall be an effective follow-up programme.

3.4.2. Items for self-inspection: Written instructions for self-inspection, shall be established to provide a minimum and uniform standard of requirements and shall include questionnaires on good manufacturing practices requirements covering at least the following items, namely: -- (a) personnel;

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

3.4.3. Self-inspection team: Management shall appoint a self-inspection team of members from inside or outside the company who are expert in the field of inspection and familiar with good manufacturing practices.

3.4.4. Frequency of self-inspection: The frequency at which self-inspections are conducted may depend on company requirements but it shall be at least once every year.

3.4.5. Self-inspection report: A report shall be made at the completion of self-inspection which shall include: --

- (a) Self-inspection results; (b)
- Evaluation and conclusions;
- and (c) Recommended corrective actions.

3.4.6. Follow-up-actions: The company management shall evaluate both the self-inspection report and the corrective actions as are necessary.

3.5. Quality audit

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

3.5.2. Supplier's audits: The quality control department shall have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

- 3.6. Complaints:
- 3.6.1. Review of complaints: All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures.
 - 3.6.2. Person authorized: A person responsible for handling the complaints and deciding the measures to be taken shall be designated, together with sufficient supporting staff to assist him and if this person is different from the authorized person, the latter shall be made aware of any complaint, investigation, or recall.
 - 3.6.3. Written procedures: There shall be written procedures describing the action to be taken including the need to consider, a recall, in the case of a complaint concerning a possible product defect.
 - 3.6.4. Recording defects and investigation: Any complaint concerning a product defect shall be recorded with all the original details and thoroughly investigated. The person responsible for quality control shall normally be involved in the study of such problems.
 - 3.6.5. Investigation: If a product defect is discovered or suspected in a batch, consideration shall be given to whether other batches shall be checked in order to determine whether they are also affected, in particular, other batches that may contain reprocessed product from the defective batch shall be investigated.
 - 3.6.6. Follow-up action: Where necessary, appropriate follow-up action, possibly including product recall, shall be taken after investigation and evaluation of the complaint.
 - 3.6.7. Recording measures: All the decisions and measures taken as a result of complaint shall be recorded and referenced to the corresponding batch records.
 - 3.6.8. Review for recurring problems: Complaint record shall be regularly reviewed for any indication of specific or recurring problems that require attention.
- 3.7. Product recalls:
- 3.7.1. System: There shall be a system to promptly and effectively recall from the market the products known or suspected to be defective.
 - 3.7.2. Authorized person: A person responsible for the execution and coordination of recalls shall be designated, as well as sufficient staff to handle shall aspects of the recalls with the appropriate degree of urgency, this person shall normally be independent of the sales and marketing organization; if this person is different from the authorized person, the latter shall be made aware of any recall operation.
 - 3.7.3. Written procedure: There shall be established written procedures, regularly checked and updated for the organization of any recall activity. Recall operations shall be capable of being initiated promptly at least down to the level of the health institutions and all sale channels including whole sale and where possible retail sale and public notice if required.
 - 3.7.4. Recall with promptness: All competent authorities to whom a given product may have been distributed shall be promptly informed of any intention to recall the product because it is, or was suspected of being, defective.
 - 3.7.5. Distribution records: The distribution records shall be readily available to the person(s) responsible for recalls, and they shall contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received "samples for clinical tests and medical samples) to permit an effective recall.
 - 3.7.6. Recording of progress: The progress of the recall process shall, be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the products.
 - 3.7.7. Evaluation: The effectiveness of the arrangements for recalls shall be evaluated from time to time.

- 3.7.8. Storage of recalled drugs: An instruction shall be included to store recalled products in a secure segregated area while their fate is decided.
- 3.7.9. All concerned to be informed: The Central Licensing and Registration Boards and other concerned Government authorities shall be immediately informed if it is intended to recall product(s) or if a product has been recalled. Effective system shall be maintained to inform the doctors, pharmacist and public of the recalled products.

Section – 4

4. Personnel

4.1. General: The licensee shall provide: -

- (a) Sufficient qualified personnel to fulfil all its responsibilities required under these rules; and
- (b) Organization chart.

4.2. Written duties: All responsible staff shall have their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. There shall be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of good manufacturing practices. Individuals responsibilities shall be clearly understood by the individuals concerned.

4.3. Good manufacturing practices awareness: All personnel shall be aware of the principles of good manufacturing practices that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

4.4. Prohibition of unauthorized persons: Steps shall be taken to prevent unauthorized people from entering production, storage, and quality control areas, and personnel who do not work in these areas shall not use them as a passageway.

4.5. Duties of heads of departments: The heads of the production and quality control departments may have shared, or jointly exercised the following responsibilities relating to quality, namely: --

- (a) the authorization of written procedures and other documents, including amendments;
- (b) the monitoring and control of the manufacturing environment;
- (c) plant hygiene;
- (d) process validation and calibration of analytical apparatus;
- (e) training, including the application and principles of quality assurance;
- (f) the approval and monitoring of suppliers of materials;
- (g) the approval and monitoring of contract manufacturers;
- (h) the designation and monitoring of storage conditions for materials and products;
- (i) the retention of records;
- (j) the monitoring of compliance with good manufacturing practices requirements; and
- (k) the inspection, investigation, and taking of samples in order to monitor factors that may affect product quality.

4.6. Duties of production incharge: The head of the production department may have the following responsibilities, namely: --

- (a) to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
- (b) to approve the instructions relating to production operations including the inprocess controls, and to ensure their strict implementation;

- (c) to ensure that the production records are evaluated and signed by a designated person before they are made available to the quality control department;
- (d) to check the maintenance of the department, premises, and equipment;
- (e) to ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available; and
- (f) to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

4.7. Duties of Quality Control Incharge: The head of the quality control department shall have the following responsibilities, namely: --

- (a) To approve or reject starting materials, packaging materials, and intermediate, bulk, and finished products;
- (b) To evaluate batch records;
- (c) To ensure that all necessary testing is carried out;
- (d) To approve sampling instructions, specifications, test methods, and other quality control procedures;
- (e) To approve and monitor analyses carried out under contract;
- (f) To check to the maintenance of the department, premises and equipment;
- (g) To ensure that the appropriate validations, including those of analytical procedures and calibrations of control equipment are done; and
- (h) To ensure that the required initial and continuing training of, quality control personnel is carried out and adapted according to need.

4.8. Training:

4.8.1. Written programme: The training shall be provided in accordance with a written programme for all the personnel whose duties require them to work in the production areas, as the case may be, in the control laboratories (including the technical, maintenance, and cleaning personnel), and for other personnel whose activities could affect the quality of the products.

4.8.2. Training appropriate to duties: Besides basic training on the theory and practice of good manufacturing practices, newly recruited personnel shall receive training appropriate to the duties assigned to them, continuing training shall also be given, and its practical effectiveness shall be periodically assessed, training programmes shall be available, approved by the head of either production or quality control, as appropriate, and training records shall be kept.

4.8.3. Specific training: Personnel working in areas where contamination is a hazards, such as clean areas or areas where highly active, toxic, infectious, or sensitizing materials are handled, shall be given specific training.

4.8.4. Understanding concepts: The concept of quality assurance and all the measures capable of improving its understanding and implementation shall be fully discussed during the training sessions.

4.8.5. Visitors or untrained personnel discouraged: Visitors or untrained personnel shall be discouraged entry into the production and quality control areas.

4.9. Personal hygiene:

4.9.1. Health Examination: All personnel, prior to and during employment, as may be appropriate, shall undergo health examinations and personnel conducting visual inspections shall also undergo periodic eye-examinations.

4.9.2. Practices in personal hygiene: All personnel shall be trained in hygiene shall be observed by all those concerned with manufacturing processes, personnel shall be instructed particularly to wash their hands before entering production areas, and signs to this effect shall be pasted and instructions observed.

4.9.3. Illness: 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 starting materials, packaging materials, in-process materials, or drug products until the condition is no longer judged to be a risk.

4.9.4. Reporting health problems: All employees shall be instructed and encouraged to report to their immediate supervisor any conditions, relating to plant, equipment, or personnel, that they consider may adversely affect the products.

4.9.5. Avoiding direct contact with materials: Direct contact shall be avoided between the operator's hands and starting materials, primary packaging materials, and intermediate or bulk product.

4.9.6. Appropriate clothings and covering: To ensure protection of the product from contamination, personnel shall wear clean body coverings appropriate to the duties they perform, including appropriate hair covering, and used clothes, if reusable, shall be stored in separate closed containers until prepared laundered and, if necessary, disinfected or sterilized.

4.9.7. Foods and drinks prohibited: Smoking, eating, drinking chewing, and keeping plants, food, drink, smoking material and personal medicines shall not be permitted in production, laboratory, and storage areas or in any others areas where they might adversely influence product quality.

SECTION-5

GOOD PRACTICES IN MANUFACTURING PROCESSING

5.1. General responsibility of licensee: The licensee shall follow Good Manufacturing Practices in production of drugs under which it shall be ensured that: -

- (a) all manufacturing processes which shall be defined are systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;
- (b) critical steps of manufacturing processes and any significant changes made to the processes are validate;
- (c) all necessary facilities are continued to be made available, including:--
 - (i) appropriately qualified and trained personnel;
 - (ii) adequate premises and space;
 - (iii) suitable equipment and services;
 - (iv) correct materials, containers, and labels;

- (v) approved procedures and instructions;
- (vi) suitable storage and transport; and
- (vii) adequate personnel laboratories, and equipment for in-process controls under the responsibility of the production management.
- (d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided and followed in letter and spirit;
- (e) operators receive training and refresher courses at regular intervals to carry out procedures correctly, and records of such training are maintained;
- (f) records are made, manually and or by recording instruments, during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected, and any significant deviations are fully recorded and investigated;
- (g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
- (h) the proper storage and distribution of the products minimizes any risk to their quality; and
- (i) the written system to recall any batch of product from sale or supply is followed whenever a recall is necessitated.

SECTION-6

MATERIALS

6.1. Material, general

- 6.0.1. Quarantine: All incoming materials and finished products shall be quarantined immediately after receipt or processing, until they are released for use or distribution.
- 6.0.2. Appropriate storage: All materials and products shall be stored under the appropriate conditions established by the manufacturer and in an orderly manner to permit batch segregation and stock rotation by a first-in, first-out rule.

6.2. Starting materials

- 6.2.1. Purchase: The purchase of starting materials is an important operation that must involve staff who have a particular and thorough knowledge of the products and suppliers and a pharmacist with some experience of production may be preferred.
- 6.2.2. Purchase from producer or established suppliers: Starting materials shall be purchased directly from the producer or only from established suppliers.
- 6.2.3. Checking of containers: For each consignment, the containers shall be checked for integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels; and, containers shall be cleaned where necessary and labelled, if required, with the prescribed data.
- 6.2.4. Damaged container: Damage to containers and any other problem that might adversely affect the quality of a material shall be recorded and reported to the quality control department and investigated.
- 6.2.5. Delivery from different batches: If a delivery of material is made up of different batches, each batch shall be considered as separate for sampling, testing, and release.

- 6.2.6. Labelling: Starting materials in the storage-area shall be appropriately labelled, and labels shall bear at least the following information, namely: --
- (a) the designated name of the product and the internal code reference where applicable.
 - (b) The batch number(s) given by the supplier and on receipt by the manufacturer, if any;
 - (c) Where appropriate, the status of the contents such as on quarantine, on test, released, rejected returned, and recalled, and
 - (d) Where appropriate an expiry date or a date beyond which retesting is necessary. When fully computerized storage systems are used appropriate system shall be developed for the identification of above-referred information.
- 6.2.7. Identity of contents: There shall be appropriate procedures or measures to ensure the identity of the contents of each container of starting material, and bulk containers from which samples have been drawn shall be identified.
- 6.2.8. Released materials to be used: only starting materials released by the quality control department and within their shelf-life shall be used.
- 6.2.9. Correct dispensing: Starting materials shall be dispensed only by designated persons, following a written procedure to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.
- 6.2.10. Checking: Each dispensed material and its weight or volume shall be independently checked and the check recorded.
- 6.2.11. Labelling: Materials dispensed for each batch of the final product shall be kept together and conspicuously labelled as such.

6.3. Packaging materials

- 6.3.1. Purchase: The purchase, handling and control of primary and printed packaging materials shall be as for starting materials.
- 6.3.2. Printed materials: Particular attention shall be paid to printed packaging materials which shall be stored in secure conditions so as to exclude the possibility of unauthorized access, cut labels and other loose printed materials shall be stored and transported in separate closed containers so as to avoid mixups and packaging materials shall be issued for use only by designated personnel following an approved and documented procedure.
- 6.3.3. Reference numbers: Each delivery or batch of printed or primary packaging material shall be given a specific reference number or identification mark.
- 6.3.4. Obsolete materials: Outdated or obsolete primary packaging material or printed packaging material shall be destroyed and its disposal be recorded.
- 6.3.5. Checking before delivery: All products and packaging materials to be used shall be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.

6.4. Intermediate and bulk products

- 6.4.1. Storage: Intermediate and bulk products shall be kept under appropriate conditions.
- 6.4.2. Handling: Intermediate and bulk products purchased as such shall be handled on receipt as though they were starting materials.

6.5. Finished pharmaceutical products

- 6.5.1. Quarantine: Finished pharmaceutical products shall be held in quarantine until their final release, and thereafter they shall be stored as usable stock under conditions established by the manufacturer.

- 6.5.2. Release: The evaluation of finished products and the documentation necessary for release of a product for sale, as per requirement of these rules, shall be followed.
- 6.6. Rejected and recovered materials
- 6.6.1. Storage and disposal: Rejected materials and products shall be clearly marked as such and stored separately in restricted areas, and they shall either be returned to the suppliers or, where appropriate, reprocessed or destroyed and then action shall be approved by authorized personnel and recorded.
- 6.6.2. Reprocessing: The reprocessing of rejected products shall be exceptional, it is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved and record shall be kept of the reprocessing and a reprocessed batch shall be given a new batch number.
- 6.6.3. Batch recovery: The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture shall be authorized beforehand, this recovery shall be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life and the recovery shall be recorded.
- 6.6.4. Additional testing of reprocessed materials: The need for additional testing of any finished product that has been reprocessed, or into which a recovered product has been incorporated, shall be considered by the quality control department.
- 6.7. Recalled and returned products
- 6.7.1. Recalled products: Recalled products shall be identified, clearly marked as such and stored separately in a secure area until a decision is taken on their fate.
- 6.7.2. Returned goods: Products returned from the market shall be destroyed unless it is certain that their quality is satisfactory, they may be considered for resale, relabelling, or bulking with a subsequent batch only after they have been critically assessed by the quality control department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued shall be taken into account in this assessment, where any doubt arises over the quality of the product, it shall not be considered suitable for reissue or re-use, although basic chemical reprocessing to recover the active ingredient may be possible, and any action taken shall be appropriately recorded.
- 6.8. Reagents and culture media
- 6.8.1. All reagents and culture media shall be recorded upon receipt or preparation.
- 6.8.2. Reagents made up in the laboratory shall be prepared according to written procedures and appropriately labelled, the label shall indicate the concentration, standardization factor, shelf-life, the date when re-standardization is due, and the storage conditions and the label shall be signed and dated by the person preparing the reagent.
- 6.8.3. Both positive and negative controls shall be applied to verify the suitability of culture media and the size of the inoculums used in positive controls shall be appropriate to the sensitivity required.
- 6.9. Reference standards
- 6.9.1. Testing of prepared reference standard: Reference standards may be available in the form of official reference standards and reference standards prepared by the producer shall be tested, released, and then stored in the same way as official standards, and they shall be kept under the responsibility of a designated person in a secured area.

- 6.9.2. Use: Official reference standards shall be used only for the purpose described in the appropriate testing method submitted for registration purposes.
- 6.9.3. Working standards: Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization, and all in house reference standards shall be based on official reference standards, when available.
- 6.9.4. Storage: All reference standards shall be stored and used in a manner that will not adversely affect their quality.
- 6.10. Waste materials
 - 6.10.1. Storage: Provision shall be made for the proper and safe storage of waste materials awaiting disposal, and toxic substances and flammable materials shall be stored in suitably designed and separate enclosed cupboards.
 - 6.10.2. Disposal: Waste material shall not be allowed to accumulate, and it shall be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.
 - 6.10.3. Effluent Control: There shall be an effluent control system.
- 6.11. Miscellaneous

Rodenticides, insecticides, fumigating agents, and sanitizing materials shall not be permitted to contaminate equipment, starting materials, packaging materials, inprocess materials, or finished products.

SECTION-7

- 7.1. Processing Operations
 - 7.1.1. General: Production operations must follow clearly defined procedures with the objective of obtaining products of the requisite quality.
 - 7.1.2. Material handling: All handling of materials and products such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging, and distribution shall be done in accordance with written procedures or instructions and where necessary, recorded.
 - 7.1.3. Avoiding deviation: Any deviation from instructions or procedures shall be avoided as far as possible and if deviations occur, they shall be approved in writing by a designated person, with the involvement of the quality control department.
 - 7.1.4. Yield checks: Check on yields and re-conciliation of quantities shall be carried out as necessary to ensure that yields are within acceptable limits.
 - 7.1.5. Avoiding mix-ups: Operations on different products shall not be carried out simultaneously or consecutively in the same room unless there is no risk of mixup or cross-contamination.
 - 7.1.6. Labelling: At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate the rooms used shall be labelled or otherwise identified with an indication of the product or material being processed and its strength, where applicable, and the batch number, and where applicable this indication shall mention the stage of production.
 - 7.1.7. Un-authorized entry prohibited: Access to the production premises shall be restricted to authorized personnel.
 - 7.1.8. In process controls: In process controls are mostly performed within the production area and they shall not carry any risk for the quality of the product.
- 7.2. Prevention of cross-contamination and bacterial contamination in production.

- 7.2.1. Precautions against dust: When dry materials and products are used in production, special precautions shall be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitizing materials.
- 7.2.2. Measures against contamination: Contamination of a starting material or of a product by another material or product shall also be avoided and similarly, crosscontamination shall be avoided by appropriate technical or organizational measures, as may be necessary by conducting production segregated areas, namely:-
- (a) conducting production in segregated areas;
 - (b) providing appropriate airlock, pressure differentials and dust extraction;
 - (c) minimizing the risk of contamination caused by re-circulation or re-entry of untreated or insufficiently treated air;
 - (d) wearing and keeping protective clothing in areas where products with special risk of cross-contamination are processed;
 - (e) using, cleaning and decontamination procedures of known effectiveness, as in-effective cleaning of equipment is a common source of crosscontamination;
 - (f) encourage using a “closed system” of production;
 - (g) testing for residues where necessary;
 - (h) using cleanliness status labels on equipment, showing the name of the previous product.
- 7.2.3. Cross-contamination checks: Measures to prevent cross-contamination and their effectiveness shall be checked periodically according to standard operating procedures.
- 7.2.4. Microbiological monitoring: Production areas where susceptible products are processed shall undergo periodic microbiological monitoring and the bio-burden shall be kept within the specified limits.
- 7.3. Processing operations, intermediate and bulk products
- 7.3.1. Pre-processing cleanliness checks: Before any processing operation is started, steps shall be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, legal, or documents not required for the current operation.
- 7.3.2. In-process controls: Necessary in-process controls and environmental controls shall be carried out and recorded.
- 7.3.3. Defective equipment: Means shall be instituted for indicating failures of equipment of services, such as water of gas, to equipment. Defective equipment shall be withdrawn from used until the defect has been rectified.
- 7.3.4. Cleaning containers: Containers for filling shall be cleaned before filling and attention shall be given to avoiding and removing any contaminants such as glass fragments and metal particles. Production equipment shall be cleaned according to detailed written procedures and stored only under clean and dry conditions.
- 7.3.5. Yield deviations: Any significant deviation from the expected yield shall be recorded, and investigated.
- 7.3.6. Product pipelines: Checks shall be carried out to ensure that pipelines and other pieces and equipment used for the transportation of product from one area to another area connected in correct manner.
- 7.3.7. Water Pipes: Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes shall be sanitized according to written procedures that detail the action and limits for microbiological contamination and the measures to be taken.

- 7.3.8. Equipment calibration: Measuring, weighing, recording control equipment and instruments shall be serviced and calibrated at pre-specified intervals and records maintained. To ensure satisfactory functioning instruments shall be checked daily or prior to use for performing analytical tests and the date of calibration and the date when re-calibration is due shall be clearly indicated.
- 7.3.9. Repair and maintenance: Repair and maintenance operations shall not present any hazard to the quality of the products.
- 7.4. Packaging operations
- 7.4.1. Avoiding mix-ups: When the programme for packaging operations is being set up particular attention shall be given to minimizing the risk of cross-contamination, mix-up, or substitutions, and different products shall not be packaged in close proximity unless there is physical segregation or the use of electronic surveillance.
- 7.4.2. Pre- packaging checks: Before packaging operations are begun, steps shall be taken to ensure that the work area, packaging lines, printing machines, and other, equipment are clean and free from any products, materials, or documents previously used and not required for the current operation, and the line clearance shall be performed according to an appropriate checklist and recorded.
- 7.4.3. Labelling of packaging line: The name and batch number of the product being handled shall be displayed at each packaging station or line.
- 7.4.4. Process continuity: Normally, filling and sealing shall be followed as quickly as possible by labelling and if labelling is delayed, appropriate procedures shall be applied to ensure that no mix-up or mix-labelling can occur.
- 7.4.5. Printing operation checks: The correct performance of any printing, code numbers or expiry dates, done separately or in the course of the packaging shall be checked and recorded, and attention shall be paid to printing by hand which shall be re-checked at regular intervals.
- 7.4.6. Label verification: Special care shall be taken when cut labels are used and when over-printing is carried out off-line and in-hand packaging operations, roll-feed labels are normally preferable to cut labels in helping to avoid mix-up. On-line verification of all labels by automated electronic means can be helpful in preventing mix-up, but checks shall be made to ensure that electronic code readers, label counters, or similar devices are operating correctly.
- 7.4.7. Fast colour printing on labels: Printed and embossed information on packaging materials shall be distinct and resistant to fading or erasing.
- 7.4.8. On-line packaging checks: On-line control of the product during packaging shall include at least check on: --
- (a) The general appearance of the packages;
 - (b) Whether the packages are complete;
 - (c) Whether the correct product and packaging materials are used;
 - (d) Whether any over-printing is correct;
 - (e) The correct functioning the line monitors; and
 - (f) Samples taken from the packaging line shall not be returned unless inspection is done in close the packaging proximity of line.
- 7.4.9. Product re-introduction on packaging line: Products that have been involved in an unusual event during packaging shall be re-introduced into the process only after special inspection, investigation, and approval by authorized personnel and a detailed record shall be kept of this operation.
- 7.4.10. Discrepancies to be investigated: Any Significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced shall be investigated and satisfactorily accounted for before released.

- 7.4.11. Destruction of un-used packaging materials: Upon completion of a packaging operation, un-used batch-coded packaging materials shall be destroyed and the destruction recorded, and a documented procedure shall be followed if encoded printed materials are returned to stock.

SECTION-8

8. Sanitation and hygiene

Genera: A high level of sanitation and hygiene shall be practiced in every aspect of the manufacture of drug products, the scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product, and potential sources of contamination shall be eliminated through an integrated comprehensive programme of sanitation and hygiene.

SECTION-9

9. Validation

9.1. General: Validation studies shall be conducted in accordance with predefined protocols. A written report summarizing recorded results and conclusions shall be prepared and stored. Processes and procedures shall be established on the basis of a validation study and undergo periodic re-validation to ensure that they remain capable of achieving the intended results, and particular attention shall be accorded to the validation of processing, testing and cleaning procedures.

9.2 Process Validation to be performed as per written procedures

- 9.2.1. Validation of critical processes: Critical process shall be validated, prospectively or retrospectively.
- 9.2.2. Validation of new master formula: When any new master formula or method of preparation is adopted, steps shall be taken to demonstrate its suitability for routine processing, and, the defined process, using the materials and equipment specified, shall be shown to yield a product consistently of the required quality.
- 9.2.3. Validation of equipment and materials: Significant amendments to the manufacturing process, including any changer in equipment or materials that may affect product quality and or the reproducibility of the process shall be validated.

SECTION-10

10. Documents

- 10.1.1. Maintenance of documents: Documents, as required under these rules, shall be meticulously maintained and regularly reviewed and kept up to date, and when a document has been revised, a system shall exist to prevent inadvertent use of the superseded version.
- 10.1.2. Records of action: Records of action: Records shall be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. The batch record shall be retained for at least one year after the expiry date of the finished product.

- 10.1.3. Documentation systems: Data may be recorded by electronic data processing systems or by photographic or other reliable means. Master formulate and detailed standard operating procedures relating to the system in use shall be available and the accuracy of the records shall be checked and its documentation is handled by electronic data-processing methods, only authorized persons shall be able to enter or modify data in the computer, and there shall be a record of changes and deletions, access shall be restricted by passwords or other means and the entry of critical data shall be independently checked and data shall also be readily available.
- 10.1.4. States identification: Labels applied to containers, equipment, or premises shall be unambiguous and in the company's agreed format. The labels of different colours may also be used in addition to the wording to indicate the status such as "quarantined" "Accepted," "rejected," or "clear".
- 10.1.5. Product labelling: All finished products shall be labelled in accordance with the Drugs (Labelling and Packing) Rules, 1986.
- 10.1.6. Reference standards identification: For reference standards, the label or accompanying documents shall indicate concentration, date of manufacture, expiry, date, and storage conditions, where appropriate.
- 10.1.7. Specification approvals: Each specification shall be approved and maintained by the quality control unit.
- 10.1.8. Revision of specification: Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia or the Drugs (Specifications) Rules, 1978.
- 10.1.9. Packaging material specifications: Packaging material shall conform to specifications, with emphasis placed on the compatibility of the material with the drug product it contains.
- 10.1.10. Starting material re-assay: Documents describing testing procedures shall state the required frequency for re-assaying each starting material, as determined by its stability.
- 10.2. Specification for Intermediate and bulk products

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

10.3. Batch processing records

- 10.3.1. General: A batch processing record shall be kept for each batch processed based on the relevant parts of the currently approved master formula, and the method of preparation of such records shall be designed to avoid transcription errors.
- 10.3.2. Checking work station: Before any processing begins, a check shall be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use, and this check shall be recorded.
- 10.3.3. Recording process operation: During processing, the following information shall be recorded at the time each action is taken, and after completion the record shall be dated and signed by the person responsible for the processing operations, namely:-
 - (a) the name of the product;
 - (b) the number of the batch being manufactured;
 - (c) date and times of commencement of significant intermediate stages, and of completion of production;
 - (d) the name of the person responsible for each stage of production;

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

10.4. Batch packaging records

10.4.1. General: A batch packaging record shall be kept for each batch or part batch processed based on the relevant parts of the packaging instructions, and the method of preparing such records shall be designed to avoid transcription errors.

10.4.2. Pre-packaging line checks: Before any packaging operation begins, checks shall be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks shall be recorded.

10.4.3. Recording of packaging operation: The following information shall be recorded at the time each action is taken, and the date and the person responsible shall be clearly identified by signature or electronic password, namely: --

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

- 10.4.4. Recording batch number: Batch-number allocation shall be immediately recorded in a logbook, and the record shall include date of allocation, product identity, and size of batch.
- 10.4.5. Analytical records: Analysis records shall include at least the following, namely:-
- - (a) the name of the material or product and, where applicable, dosage form;
 - (b) the batch number and, where appropriate, the manufacturer and/or supplier;
 - (c) references to the relevant specifications and testing procedures;
 - (d) test results, including observations and calculations, and reference to any specifications (limits);
 - (e) dates of testing;
 - (f) the initials of the persons who performed the testing;
 - (g) the initials of the persons who verified the testing and the calculations, where appropriate; and
 - (h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.
- 10.4.6. Finished product release procedure: Written release and rejection procedures shall be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.
- 10.4.7. Recording batch distribution: Records shall be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.
- 10.4.8. Standard operating procedures: Standard operating procedures and associated records of action taken or, where appropriate, conclusions reached shall be available at the premises for: --
- (a) equipment assembly and validation;
 - (b) analytical apparatus and calibration;
 - (c) maintenance, cleaning, and sanitization;
 - (d) personnel matters including qualification, training clothing, and hygiene;
 - (e) environmental monitoring;
 - (f) pest control;
 - (g) complaints; (h) recalls; and (i) returns.
- 10.4.9. Equipment logbooks: Logbooks shall be kept with major and critical equipment as identified by the licensee and shall record, as appropriate, any validations, calibrations, maintenance, cleaning, or repair operations including dates and the identity of the people who carried out these operations.
- 10.4.10. Equipment utilization record: The use of major and critical equipment and the areas where products have been process shall be appropriately recorded in chronological order.

PART II

ADDITIONAL CONDITIONS FOR MANUFACTURE OF STERILE PRODUCTS

In addition to the general conditions for manufacture of drugs by way of formulation as described in Part-II of this guidance document, the following additional conditions shall be followed for the manufacture of sterile products.

SECTION-I

1. General

1.1. The production of sterile preparations shall be carried out in clean areas, entry to which shall be through airlocks for personnel and/or for goods clean areas shall 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 shall 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 as given in the table below:-

TABLE

Air classification system for manufacture of sterile products

Maximum number of particles permitted per m ³		Maximum number of viable microorganisms permitted per m ³	
Grade	0.5-5µm	75µm	
A (laminar-airflow workstation)	3500	None	Less than 1
B	3500	None	5
C	350000	2000	100
D	3500000	200000	500

Notes:--

* Laminar-airflow systems shall provide a homogeneous air speed of about 0.30 ± 20 per cent. M/s for vertical flow and about 0.45 ± 25 per cent. M/s for horizontal flow but precise air speeds will depend on the type of equipment.

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

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

* The guidance given for the maximum permitted number of particles corresponds approximately to the United States Federal Standard 209 E as follow:

Class 100 (Grades A and 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.

1.4. Area Grade: Area grades must be selected by the manufacturer on the basis of validation runs (e.g., sterile media fills) as identified below.

2. Manufacture of sterile preparation

2.1. Manufacturing Operations Classifications are here divided into three categories:

(a) Terminally sterilized products: Those in which the preparation is sealed in its final container and terminally sterilized;

(b) Products sterilized by filtration: The preparation is sterilized by filtration;

(c) Products manufactured under aseptic conditions: Those in which the preparation can be sterilized neither by filtration nor terminally and consequently must be produced from sterile starting materials in an aseptic way.

2.2. Terminally sterilized products: Solutions shall 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 are taken to minimize contamination, such as the use of closed vessels. For parenteral, filling shall 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 shall generally be done in a Grade C environment before terminal sterilization.

2.3. Products sterilized by filtration: The handling of starting materials and the preparation of solutions shall be done in a Grade Environment. These activities could be allowed in a Grade D environment if additional measures are 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.

2.4. Products manufactured under aseptic conditions: The handling of starting materials and all further processing shall be done in a Grade A or B area with a Grade B or C background respectively.

3. Personnel

3.1. General: Only the minimum number of personnel required shall be present in clean areas, and it is particularly important during aseptic processes. Inspections and control shall be conducted from outside the areas as far as possible.

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

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

3.4. Hygiene and cleanliness: High standards of personal hygiene and cleanliness are essential and personnel involved in the manufacture of sterile preparations shall be instructed

to report apparent illness or open lesion. Periodic health checks for such conditions are desirable, and actions to be taken about personnel who could be introducing undue microbiological hazard shall be decided by a designated competent person.

3.5 Use of protective garments: Outdoor clothing shall not be brought into the clean areas, personnel entering the changing rooms shall already be clad in standard factory protective garments and changing and washing shall follow a written procedure.

3.6. Clothing requirements: The clothing and its quality shall be appropriate for the process in such a way so as to protect the product from contamination.

3.7. Protective Garments in grade B room: For every worker in a Grade B room, clean sterilized protective garments shall be provided at each work session, or at least once a day if monitoring results justify it, the gloves shall be regularly disinfected during operations, masks and gloves shall be changed at least at every working session, and the use of disposable clothing may be followed where possible.

3.8. Washing of clothing: Clothing used in clean areas, shall be washed or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. Separate laundry facilities for such clothing are desirable. If fibres are damaged by inappropriate cleaning or sterilization there may be an increased risk of shedding particles. Washing and sterilization operations shall follow standard operating procedures.

3.9. Prohibitions: Wrist-watches and jewellery shall not be worn in clean areas, and cosmetics that can shed particles shall not be used, clothing shall be appropriate to the air grade of the area where the personnel will be working, and the description of clothing required for each grade is given below:

- Grade D: The hair and, where appropriate, beard shall be covered, protective clothing and appropriate shoes or long shoes shall be worn, and appropriate measures shall be taken to avoid any contamination coming from outside the clean area.
- Grade C: The hair and, where appropriate, beard shall be covered, a shingle or twopiece trouser suit, gathered at the wrists and with a high neck and appropriate shoes or overshoes, shall be worn, and the clothing, shall shed virtually no fibres or particulate matter.
- Grade B: Headgear shall totally enclose the hair and, where appropriate, beard; it shall be tucked into the neck of the short, a face mask shall be worn to prevent the shedding of droplets; sterilized non-powdered rubber or plastic gloves and sterilized or disinfected footwear shall be worn; trouser-bottoms shall be tucked inside the footwear and garment sleeves into the gloves, and the protective clothing shall shed virtually no fibres or particulate matter and shall retain particles shed by the body.

SECTION-2

4. Maintenance of clean area

4.1. General: 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 1.3 gives the minimum air grades required for different manufacturing operations. The particulate and microbiological conditions as prescribed shall be maintained in the zone immediately surrounding the product whenever the product is exposed to the environment. These conditions shall 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 shall 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, and when such techniques are used the recommendations relating to air quality and monitoring, still apply, with appropriate interpretations of the terms “workstation” and environment.

4.2 Airlock system: The entry to the sterile production areas shall be through airlocks for personal and / or for materials. Airlock doors shall not be opened simultaneously, and an interlocking system and a visual and / or audible warning system where appropriate shall be operated to prevent the opening of more than one door at a time.

4.3. Air supply system: A filtered air supply system of appropriate efficiency shall maintain a positive pressure relative to surrounding area under all operational conditions and flush the area effectively. Moreover, particular attention shall be paid to the protection of the zone greatest risk that is, the immediate environment to which the product and the cleaned components in contact with it are exposed, and the various recommendations regarding air supplies and pressure differentials may need to be modified if it becomes necessary to contain materials such as pathogenic, highly toxic, radioactive, or live viral or bacterial materials. Decontamination facilities and the treatment of air leaving a clean area may be necessary for some operations.

4.4. Maintenance of equipment: When equipment maintenance is carried within the clean area, clean instruments and tools shall be used, and the area shall 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.

4.5 Water supply: Water treatment plants shall not be operated beyond their designed capacity and water shall be produced, stored and distributed in a manner that prevents microbial growth for example by constant circulation at 90°C or at temperature validated to keep microbial count of water within the limit.

6. Sanitation

6.1 Procedure: The sanitation of clean areas is particularly important, they shall be cleaned frequently and thoroughly in accordance with a written programme approved by the quality control department, where disinfectants are used, more than one type shall be employed with periodic alterations, the monitoring shall be regularly undertaken in order to detect the emergence of resistant strains of micro-organisms, and in view of its limited effectiveness, ultraviolet light shall not be used as a substitute for chemical disinfection.

6.2. Use of disinfectants and detergents: Disinfectants and detergents shall be monitored for microbial contamination. Dilutions shall be kept in previously cleaned container and shall not be stored for long periods unless sterilized, and partly emptied containers shall be topped up.

6.3 Fumigation: Fumigation of clean areas may be useful for reducing microbiological contamination in inaccessible places, if required.

6.4. Monitoring of clean areas: Clean areas shall be monitored at planned intervals during operations by means of microbial counts of air and surfaces, where aseptic operations are performed, monitoring shall be frequent to ensure that the environment is within specifications, the results of monitoring shall be considered when batches are assessed for approval, air particulate quality shall also be evaluated on a regular basis, and additional monitoring is sometimes desirable even when there are no production operations such as after validation of systems, cleaning and fumigation.

SECTION-5

7. Processing

7.1. Precautions against contamination: Precautions to minimize contamination shall be taken during all processing stages including the stages before sterilization.

7.2 Preparations of live organisms: Preparations containing live microbiological organisms shall not be made or containers filled in areas used for the processing of other pharmaceutical products except for validation purposes however, vaccines of dead organisms or of bacterial extracts may be dispensed into containers after validated in activation and validated cleaning procedures in the same premises as other sterile pharmaceutical products.

7.3. Simulation of aseptic operations validation: The use of nutrient media that support microbial growth in trails to simulate aseptic operations, sterile media fills and broth fills, is a valuable part of overall validation of an aseptic process, and such trials shall have the following characteristics, namely: --

- (a) They shall simulate as closely as possible actual operations, taking into account such factors as complexity of operations number of personnel working, and length of time;
- (b) the medium or media selected shall be capable of growing a wide spectrum of micro-organisms, including those that would be expected to be found in the filling environment; and
- (c) they shall 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.

Note: It is recommended that at least 3000 units of production be included in each broth-fill trial. The target shall be zero growth and anything above 0.1% of units contaminated shall be considered unacceptable. Any contamination shall be investigated. Broth fills shall be repeated at regular intervals, and whenever a significant alteration in the product, premises, equipment or process warrants revalidation. Care shall be taken that validations do not harm the processes.

7.4. Monitoring water supply sources: Water sources, water-treatment equipment and treated water shall be monitored regularly for chemicals, biological contamination and contamination with endotoxins to ensure that the water complies with the specifications appropriate to its use. Records shall be maintained of the results of the monitoring and of any action.

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

7.6. Care of starting materials: Micro-biological contamination (bioburden) of starting materials shall be minimal which shall be monitored before sterilization, and specifications shall include requirements for microbiological quality when the need for this has been indicated by monitoring.

7.7. Care against fibers: The presence of containers and materials liable to generate fibers shall be minimized in clean areas and avoided completely while aseptic work is in progress.

7.8. Care after final cleaning of materials: Components, but product containers and equipment shall handled after the final cleaning process in such a way that they are not

decontaminated, and the stage on processing of components, bulk product containers, and equipment shall be properly identified.

7.9. Interval between operations to be minimal: The interval between the washing and drying and the sterilization of components, bulk product containers, and equipment, as well as between sterilization and use, shall be as short as possible and subject to a time-limit appropriate to the validated storage conditions, similarly the time between the start of the preparation of solution and its sterilization or filtration through a bacteria-retaining filter shall be as short as possible, and maximum permissible time shall be set for each product that takes into account is composition and the prescribed method of storage.

7.10. Sterilization of gases used: Any gas that is used to purge a solution or blanket a product shall pass through a sterilization filter.

7.11. Bioburden to be minimal: the microbiological contamination of products (bioburden) shall be minimal prior to sterilization, there shall 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 parenteral, shall be passed through a micro organism relating filter, if possible immediately before the filling process, and where aqueous solutions are held in sealed vessels, any pressure-release outlets shall be protected such as by hydrophobic microbial air filters.

7.12. Asepsis of articles in clean areas: Components, bulk product containers, equipment and any other articles required in a clean area, where aseptic work is in progress, shall be sterilized and, wherever possible, passed into the area through double-ended sterilizers sealed into the wall, and other procedures that achieve the same end of not introducing contamination, such as triple wrapping, may be acceptable in some circumstances.

7.13. New processes to be validated: The efficacy of any new processing procedure shall be validated and the validation shall be repeated at regular intervals thereafter or when any significant change is made in the process or equipment.

SECTION-6

8. Sterilization

8.1 General: Sterilization can be achieved by moist or dry heat, by ethylene oxide or other suitable gaseous sterilizing agent, by filtration with subsequent aseptic filling of sterile final containers or by irradiation with ionizing radiation but not with ultraviolet radiation unless the process is thoroughly validated, each methods has its particular applications and limitations, and where possible and practicable heat sterilization is the method of choice.

8.2 Validations: All sterilization processes must be validated and particular attention shall be given when the adopted sterilization method is not in accordance with pharmacopeia or other national standards or when it is used for a preparation that is not a simple aqueous or oily solution.

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

8.4. Care for biological indicators: biological indicators shall be considered only as an additional method for monitoring the sterilization, and if they are used, strict precautions shall be taken to avoid transferring microbial contamination from them.

8.5. Sterilized not sterilized product differentiation: There shall be a clear means of differentiating products that have not been sterilized from those that have and each basket, tray, or other carrier of products or components shall be clearly labelled with the name of the material, its batch number and an indication of whether or not it has been sterilized, and indicators such as autoclave tape may be used, where appropriate, to indicate wither or not a batch, or sub-batch, has passed through a sterilization, process, but they do not give a reliable indication that the lot is, in fact, sterilize.

9. Sterilization by heat

9.1. Recording sterilization cycle: Each heat sterilization cycle shall be recorded by appropriate equipment with suitable accuracy and precision such as time and temperature chart with a suitably large scale, the temperature shall be recorded from a probe at the coolest part of the load or loaded chamber having been determined during the validation. The temperature shall preferably, be checked against a second independent temperature probe located at the same position, the chart, or a photocopy of it, shall form part of the batch record, and chemical or biological indicators may also be used but shall not take the place of physical controls.

9.2. Sufficient time allowed to reach required temperature: Sufficient time must be allowed for the whole of the load to reach the required temperature before measurement of the sterilizing time is started and this time must be determined for each type of load to be processed.

9.3. Precautions during cooling: After the high-temperature phase of a heat sterilization cycle, precautions shall be taken against contamination of a sterilized load during cooling, and any cooling fluid or gas in contact with the product shall be sterilized, unless it can be shown that any leaking container would not be approve for use.

10. Sterilization by moist heat

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

10.2. Wrapping materials: The items to be sterilized, other than products in sealed container's, shall be wrapped in a material that allows removal of air and penetration of steam but prevents recontamination after sterilization and all parts of the load shall be in a contact with water or saturated steam at the required temperature for the required time.

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

11. Sterilization by dry heat

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

12. Sterilization by radiation

12.1. General: Radiation sterilization is used mainly for the sterilizations of heat-sensitive materials, and products, many pharmaceutical products and some packaging materials are radiation-sensitive, so this method is permissible only when the absence of deleterious effect on the product has been confirmed experimentally, and ultraviolet irradiation is not acceptable method for terminal sterilization.

12.2. Outside contractor: If radiation sterilization is carried out by an outside contractor, the manufacturer has the responsibility of ensuring that the requirements of Section 12.1 are met and that the sterilization process is validated and the responsibilities of the radiation plant operator, such as the right dose, shall also be specified.

12.3. Measurement of radiation: During the sterilization procedure the radiation dose shall be measured and for this purpose, dosimeters that are independent of dose rate shall be used giving a quantitative measurement of the dose received by the product itself, dosimeters shall be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the chamber: where plastic dosimeters are used, they shall be used within the time limit of their calibration, dosimeter absorbance shall be read within a short period after exposure to radiation. Biological indicators may be used only as an additional control. Radiation-sensitive colour discs may be used to differentiate between packages that have been subjected to irradiation and those that have not; they are not indicators of successful sterilization. The information obtained shall constitute part of the batch record, and the total radiation dose shall be administered within a predetermined time span.

12.4. Validation: Validation procedures shall ensure that consideration is given to the effect of variations in the density of the packages.

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

13. Sterilization by ethylene oxide

13.1. General: Various gases, and fumigants may be used for sterilization, ethylene oxide shall be used only when no other method is practicable. During process validation it shall be shown that the gas has no damaging effect on the product and that the conditions and time allowed for degassing are such as to require any residual gas and re-action products to defined acceptable limits for the type of product or material, and these limits shall be incorporated into the specifications.

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

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

13.4. Monitoring each cycle: Each sterilization cycle shall be monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load, and the information so obtained shall form part of the batch record.

13.5. Biological indicators: Biological indicators shall be stored and used according to the manufacturer's instructions and their performance checked by positive controls.

13.6. Record maintenance: For each sterilization cycle, records shall be made of the time taken to complete the cycle of the pressure, temperature, and humidity within the chamber during the process and of the gas concentration, the pressure and temperature shall be recorded throughout the cycle on a chart and the records shall form part of the batch record.

13.7. Validation: After sterilization, the load shall be stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to fall to the defined level, and this process shall be validated.

14. Filtration of pharmaceutical products that cannot be sterilized in the final container

14.1. General: Whenever possible, products shall be sterilized in the final container preferably by heat sterilization. Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominal pore size 0.22µm or less, or with at least equivalent micro-organism-relating properties, into a previously sterilized container, such filters can remove bacteria and moulds, but not all viruses or mycoplasmas.

14.2. Using double filter layer: Owing 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 micro-organism-relating filter immediately prior to filling may be advisable and the final sterile filtration shall be carried out as close as possible to the filling point.

14.3. Eliminate fibers: Filters that shed fibers shall not be used and the use of asbestoscontaining filters shall be absolutely excluded.

14.4. Checking integrity of filters: The integrity of the filter shall 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 shall be determined during validation and any significant differences from this shall be noted and investigated. Results of these checks shall be recorded in the batch record.

14.5. Frequency of use of filter: The filter shall not be used for more than one working day unless such use has been validated.

14.6. Filter safety: The filter shall not affect the product by removal of ingredients from it or by release of substances into it.

15. finishing of sterile products

15.1 General: Containers shall be closed by appropriately validated methods and samples shall be checked for integrity according to appropriate procedures.

15.2 Use of vacuum: Containers sealed under vacuum shall be sampled and the samples tested for maintenance of that vacuum after an appropriate predetermined period.

15.3. Inspection of containers: Filled containers of parenteral products shall be inspected individually, when inspection is done visually it shall be done under suitable and controlled conditions of illumination and background, operators doing the inspection shall pass regular eyesight checks with spectacles if worn, and be allowed frequent breaks, the process shall be validated and the performance of the equipment checked at intervals.

SECTION 7

16. Quality control

16.1. Sterility testing: Samples taken for sterility testing shall be representative of the whole of the batch but shall, in particular; include samples taken from parts of the batch considered to be most at risk of contamination, such: -

- (a) for products that have been filled aseptically, samples shall include containers filled at the beginning and end of the batch and after any significant interruption of work; and
- (b) for products that have been heat sterilized in their final containers, and samples can be taken from any part of the load.

16.2. Sterility test as the last measures: The sterility test applied to the finished product shall 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.

16.3. Monitoring endotoxins: For injectable products, consideration shall be given to monitoring the water and the intermediate and finished product for endotoxins, using an established pharmacopoeial method that has been validated for each type of product, for largevolume infusion solutions, such monitoring of water or intermediates shall always be done in addition to any tests required by the Marketing authorization on the finished product, and when a sample fails a test, the cause of failure shall be investigated and remedial action taken where necessarily.

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Guidance on Particulars to Be Shown in Manufacturing Records

I. PARTICULARS TO BE SHOWN IN MANUFACTURING RECORDS

A. Substances parenteral preparation in general:

1. Serial Number.
2. Name of the drug.
3. Batch Size.
4. Batch number.
5. Date of commencement of manufacture and date when manufacture was completed.
6. Name of all ingredients, quantities required for the batch size, quantities actually used.
7. Control reference number sin respect of raw materials used in formulation.
8. Date of mixing in case of dry products, e.g., powder, powder mixture for capsule products, etc.
9. Date of granulation wherever applicable.
10. Weight of granules.
11. Date of compression in case of tablets/ date of filling in case of capsules.
12. Date of coating wherever applicable.
13. Records of test to be carried out in case of tablets as under:-- (a) Average weight every thirty minutes.
- (b) Disintegration time as often as practicable.
14. Records of readings taken to check weight variation in case of capsules.
15. Reference to Analytical Report number stating whether of standard quality or otherwise.
16. Records on the disposal of rejected batches and batches with drawn from the market.
17. Actual production and packing particulars indicating the size and quantity of finished packing.
18. Date of release of finished packing for distribution or sale.
19. In case of Hypodermic tablets and ophthalmic preparations which are required to be manufactured under aseptic conditions, records shall be maintained indicating the precautions taken during the process of manufacture to ensure that aseptic conditions are maintained.
20. Signature of the expert staff responsible for the manufacture.

B. Parenteral preparation:

1. Serial Number.
2. Name of the drug.
3. Batch Size.
4. Batch number (if bulk lot is divided into various batches and processed separately, a batch number distinctly different from that of the bulk lot should be assigned to each of the processed batch).
5. Date of commencement of manufacture and date of completion.
6. Name of all ingredients, quantities required for the lot size, quantities actually used. (All weighing and measurements shall be checked and initialled by the competent person in the section).

7. Control reference numbers in respect of raw materials used.
 8. PH of the solution wherever applicable.
 9. Date and methods of filtration.
 10. Sterility test reference on bulk batch wherever applicable. (If bulk lot is divided into various batches and processed separately, a batch number distinctly different from that of the bulk lot should be assigned to each of the processed batch.
 11. Date of filling.
 12. Records of tests employed: --
 - (a) To ensure that sealed ampules are leak-proof.
 - (b) To check the presence of foreign particles. (c) For pyrogens wherever applicable.
 13. Records of sterilisation in case of parenteral preparation which are heat sterilised including particulars of time temperature and pressure employed.
 14. Number and size of containers filed and number rejected.
 15. Reference to Analytical Report numbers stating whether of standard quality or otherwise.
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16. Records of the disposal of rejected batch and batches with-drawn from the market.
 17. Actual production and packing particulars.
 18. Date of release finished packing for distribution or sale.
 19. Particulars regarding the precautions taken during manufacture to ensure that aseptic conditions are maintained.
 20. Control reference numbers in respect of the lot of glass containers used for filling.
 21. Signature of the expert staff responsible for manufacture.

II. RECORDS OF RAW MATERIALS

Records in respect of each raw material shall be maintained indicating the quantity received, control reference numbers, the quantities issued from time to time, the names and batch Nos. of the products for the manufacture of which the quantities have been issued and the particulars relating to the proper disposal of the stocks.

III. PARTICULARS TO BE RECORDED IN THE ANALYTICAL RECORDS

- A. Tablets and capsules:
 1. Analytical report number.
 2. Name of the sample.
 3. Date of receipt of sample.
 4. Batch number.
 5. Protocols of tests applied: (a) Description.
 - (b) Identification.
 - (c) Uniformity of weight.
 - (d) Uniformity of diameter (if applicable).
 - (e) Disintegration test (time in minutes).
 - (f) Any other tests.
 - (g) Results of assay.

Note: Records regarding various tests applied (including reading and calculation) should be maintained and necessary reference to these records should be entered in serial No. 5 whenever necessary.

6. Signature of the Analyst.
7. Opinion and signature of the approved Analyst.

B. Parenteral Preparations

1. Analytical report number.
2. Name of the sample.
3. Batch number.
4. Date of receipt of sample.
5. Number of containers filled.
6. Number of container packed.
7. Protocols of tests applied. (a) Clarity.
 - (b) PH wherever applicable.
 - (c) Identificaiton.
 - (d) Volume in container.
 - (e) Sterility—(i) Bulk sample wherever applicable, (ii) container sample.
 - (f) Pyrogen test, wherever applicable.
 - (g) Toxicity test, wherever applicable.
 - (h) Any other tests.
 - (i) Results of assay.

Note: Records regarding various tests applied (including readings and calculations) should be maintained and necessary reference to these records should be entered in Serial No. 7. Wherever necessary.

8. Signature of the Analyst.
9. Opinion and signature of the approved Analyst Pyrogen Tests:-
 1. Test report number.
 2. Name of the sample.
 3. Batch number.
 4. Number of rabbits used.
 5. Weight of each rabbit.
 6. Normal temperature of each rabbit.
 7. Mean initial temperature of each rabbit.
 8. Dose and volume of solution injected into each rabbit and time of injection.
 9. Temperature of each rabbit noted at suitable intervals.
 10. Maximum temperature.
 11. Response.
 12. Summed response.
 13. Signature of the Analyst.
 14. Opinion and signature of the approved Analyst. Toxicity Test:
 1. Test report number.
 2. Name of the Sample.
 3. Batch number.
 4. Number of mice used and weight of each mouse.
 5. Strength and volume of the drug injected.

6. Date of injection.
7. Results and remarks.
8. Signature of Analyst.
9. Opinion and signature of the approved Analyst.

C. For other drugs:

1. Analytical report number.
2. Name of the sample.
3. Batch number.
4. Date of receipt of sample.
5. Protocols of tests applied: (a) Description.
(b) Identification.
(c) Any other tests.
(d) Results of assay.

Note: Particulars regarding various tests applied (including readings and calculations) shall be maintained and necessary reference to these records shall be entered in serial No. 5 wherever necessary.

6. Signature of the Analyst.
7. Opinion and signature of the approved Analyst.

D. Raw materials:

1. Serial number.
2. Name of the material.
3. Name of the manufacturer/supplier.
4. Quantity received.
5. Invoice/Challan number and date.
6. Protocols of tests applied.

Note: Particulars regarding various tests applied (including readings and calculations) shall be maintained and necessary reference to these records shall be entered in serial No. 6 wherever necessary.

E. Container, packing material, etc.:-

1. Serial number.
2. Name of the item.
3. Name of the manufacturer/ supplier.
4. Quantity received.
5. Invoice/Challan number and date.
6. Results of tests applied.

Note: Particulars regarding various tests applied shall be maintained and necessary reference to these records shall be entered serial No. 6 wherever necessary.

7. Remarks.
8. Signature of the examiner.

Note 1: The foregoing provisions represent the minimum requirements to be complied with by the licensee. The Central Licensing Board may, however, direct the nature of records to be maintained by the licensee for such drugs as are not covered by the categories described in this guidance document.

Note 2: The Central Licensing Board may permit the licensee to maintain records in such manner as are considered satisfactory, provided the basic requirements laid down in the guidance document are complied with.

Note 3: The Central Licensing Board may as its discretion direct the licensee to maintain records for such additional particulars as it may consider necessary in the circumstances of a particular case.

F. Container, packing material etc.:--

1. Analytical report number.
2. Name of sample.
3. Date of receipt of sample.
4. Date of receipt of sample.
5. Batch number.
 - (a) Description.
 - (b) Sterility test.
 - (c) Pyrogen test, where applicable.
 - (d) Bacterial Endotoxin.
 - (e) Appearance of solution.
 - (f) Acidity or alkalinity.
 - (g) Absorbance.
 - (h) Ethylene Oxide Residue.
 - (i) Silicon oil
 - (j) Reducing substances.
 - (k) Transparency.
 - (l) Extractable matters
 - (m) Tolerance on graduated capacity.
 - (n) Graduate scale.
 - (o) Piston plunger assembly.
 - (p) Dimensions and finger grip of barrels.
 - (q) Performance in terms of Dead Space, Integrated or non-integrated needles.
 - (r) Where applicable, Auto-Disable features.
 - (s) Tolerance on nominal capacity.
 - (t) Fit of the piston in barrel.
 - (u) Fiducial lines.
 - (v) Performance after shipping. (w) Any other tests.
6. Protocols of tests applied:
7. Signature of the Analyst.
8. Opinion and signature of the approved Analyst.

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