cGMP AUDIT PROFORMA

(For GMP compliance inspection)

Part 1:

1.1 General Information

Name of Manufacturer	As per DML
Physical Address	As visited and verified
Drug Manufacturing license No. and Validity (Date of application for DML renewal)	
Contact Address	Name/designation of the person authorized for correspondence/communication
Date of inspection	
Purpose of inspection	1. Panel Inspection 2. Grant of GMP certificate 3. Re-inspection after non-compliance report 4. Grant of Registration 5. Renewal of Drug Manufacturing Licence.
Name of inspector (s)	
Name of Firm's Representative (s) accompanying during inspection	Who accompanied and assisted during the course of inspection

1.2 General Information about the Unit:

A brief of company's profile, management, establishment.

1.3 Detail of manufacturing section (s)

Pharmacological Category(ies)	Dosage Form	Total Number of Registered products	Remarks (if any)
For Example: Non-antibiotic, Antibiotic, Psychotropic, Hormones, Steroid, Cephalosporin, Penicillin etc	Tablet		
Write the applicable	Capsule		

Continue…as required			

1.4 Brief History of previous inspections:

A brief about previous two years inspections (date of inspection/ Overall cGMP compliance/ Non-Compliance/ improvements).

1.5 Focus of the inspection :

GOOD MANUFACTURING PRACTICES (GMPs) FOR MANUFACTURERS. SCHEDULE B-II UNDER THE DRUGS (LICENSING, REGISTERING AND ADVERTISING) RULES 1976, FRAMED UNDER THE DRUGS ACT, 1976 (for details refer to the Schedule)

PART-I

S. No.	CONDITION	GRADING (A,B,C or D)	Remarks
	SECTION-I		
1	**GENERAL CONDITIONS**		
	Responsibility of licensee for drug's fitness for use.		
	SECTION – 2		
2	**Quality assurance system**		
	(a) drugs are designed and developed as per requirements of good manufacturing practices;		
	(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 Act 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) Procedure for self inspection and or quality audit exists and documented;		
	(j) Written Standard Operating Procedure available according to which complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures 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 exists which is independent of other departments and under the authority of a person with the required qualifications and experience and with adequate facilities.		

3.2	Basic requirements.--		
	(a) During the period of validity of license, adequate facilities, trained personnel and approved procedures are available for sampling, inspecting, testing starting materials, packaging materials, 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) Testing methods are validated;		
	(d) Records are made 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 product described in the marketing authorization.		
	(f) Records are made of the results of inspecting and testing materials and intermediate, bulk and finished products against specifications and product assessment.		
	(g) No batch of product is released for sale prior to certification by the authorized person(s) that it is in accordance with the requirement of the rules;		
	(h) Sufficient samples of starting materials and products are retained to permit future examination of the product.		
	(i) All quality control procedures are established, validated and implemented; the reference standards for substances are evaluated maintained, and stored; correct labeling 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. All these operations shall be carried out in accordance with written procedures.		
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 material 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 effect on quality.		
	(c) be taken with care to guard against contamination or mix-up. All sampling equipment that comes into contact with the material shall be clean.		
	(d) be taken with equipment which shall be cleaned and, if necessary, sterilized before and after each use and stored separately form other laboratory equipment.		
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 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 material.		
	(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 finished 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.		
	(ii) Retention of Samples.-- Retention samples from each batch of finished product shall be kept for at least one year after the expiry date.		
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, 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 program for ongoing stability determination shall be developed and implemented to include elements such as:--		
	(iii) Stability of the finished product shall be evaluated and documented prior to marketing.		
3.4	Self-inspection		
3.4.1	General.- The management shall appoint a self inspection team. 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 program. Self inspections shall be performed routinely.		
3.4.2	Items for self-inspection.- Written instructions for self-inspection shall be established to provide a minimum and uniform standard of requirements.		
3.4.3	Frequency of self-inspection.- it shall be at least once every year.		
3.4.4	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.		
3.5	Quality audit:		
3.5.1	Audit by independent specialist.- Quality audit shall be conducted		

	which consists of an examination and assessment of all or part of a quality system.		
3.2.2	Supplier's audits.- The quality control department shall have responsibility together with other relevant departments for approving suppliers.		
3.6	Complaints:		
3.6.1	Review of complaints.-- All complaints must be carefully reviewed according to written procedures.		
3.6.2	Person authorized.-- A person responsible for handling the complaints.		
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.		
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.		
3.6.6	Follow-up action.-- Where necessary, appropriate follow-up section, 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 a 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 the 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.		
3.7.3	Written procedure.--There shall be established written procedures, regularly checked and updated for the organization of any recall activity.		
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.		
3.7.5	Distribution records.-- The distribution records shall be readily available to the person(s) responsible for 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.		
SECTION--4			
4	**Personnel**		
4.1	General.-- The licensee shall provide:--		
	(a) sufficient qualified personnel (at least one technical person for each section) to fulfill 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.		
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 head of departments.-- The head of the production and quality control department 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 in-process controls, and to ensure their strict implementation;		
	(c) to ensure that the production records re 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	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 the maintenance of the department, premises and equipment;		
	(g) to ensure that the appropriate validation, 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 program 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 product.		
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 programs 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 hazard, 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	Personnel 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 the practices of personal hygiene, a high level of personal 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 down 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 clothing and covering.-- To ensure protection of the product from contamination, personnel shall war clean body coverings appropriate to the duties they perform, including appropriate hair cover, and used clothes, if re-usable, shall be stored in separate closed containers until properly 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 medicine shall not be permitted in production, laboratory, and storage areas or in any other areas where they might adversely influence product quality.		
SECTION--5 Good practices in manufacturing processing (Separate format may be used for each manufacturing section)			
5.1	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 change made to the processes are validated; (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 producers 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**		
6.1.1	Quarantine.-- All incoming materials and finished products shall be quarantined immediately after receipt or processing, until they are released for use or distribution		
6.1.2	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 supplies.-- Staring materials shall be purchased directly from the producer or only form 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 staring material, but bulk containers form which samples have been drawn shall be identified.		
6.2.8	Released materials to be used.-- Only starting materials released by or quality control department and within their self-life shall be sued.		
6.2.9	procedure to ensure that the correct materials are accurately weighted 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 mix-ups and packaging materials shall be used 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 affect, 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 all 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 stability of culture media and the size of the inoculum 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	Waster 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 a effluent control system.		
6.11	Miscellaneous Rodenticides, insecticides, fumigating agents and sanitizing materials shall not be permitted to contaminate equipment, starting materials, packaging, materials, in-process 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 mix-up 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 strengths, where applicable, and the batch number, and where		

	applicable this indication shall also 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 are 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, cross-examination shall be avoided by appropriate technical or organizational measures, as may be necessary by 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 re processed;		
	(e) using, cleaning and decontamination procedures of known effectiveness, as in-effective cleaning of equipment is a common source of cross-contamination;		
	(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 toe standard operation 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, labels, or documents not required for the current operation.		
7.3.2	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 or of services, such as water or gas, to equipment. Defective equipment shall be withdrawn from use until the defect has been rectified.		
7.3.4	Cleaning containers.-- Containers for filling shall be cleaned before filing 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 expected yield shall be recorded and investigated.		
7.3.6	Product pipelines.-- Checks shall be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one are to another are connected in a 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 present any hazard to the quality of the products.		
7.4	Packaging operations		
7.4.1	Avoiding mix-ups.-- When the program 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 labeling and if labelling is delayed, appropriate procedures shall be applied to ensure that no mix-up or mis-labelling can occur.		
7.4.5	5 Printing operation checks.-- The correct performance of any printing, mode 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	One-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 products and packaging materials are used; (d) whether any over-printing is correct; (e) the correct functioning of 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 un-usual 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 un-usual 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 release		
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** General.-- 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, product 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 program of sanitation and hygiene (For sanitation and hygiene please also refer to Section 5 of Schedule B and Section 4.9 of Schedule B-II).		
	SECTION—9		
9	**Validation**		
9.1	General.-- Validation studies shall be conducted in accordance with pre-defined 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 processes 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 stability 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 change in equipment or materials that may affect product		

	quality and or the re-productibility 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 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 if documentation is handled by electronic data-processing method, 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 their means and the entry of critical data shall be independently checked and data shall also be readily available.		
10.1.4	Staus 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 working 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 specification.-- 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	Specifications for Intermediate and bulk products Specifications for intermediate and bulk products shall be available if these are purchased or dispatched, of 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 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 explanation 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-packing line checks.-- Before any packaging operation beings, 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. There 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 for identity and conformity with the packaging instructions, including the results of in-process controls;		

	(f) details of the packaging operations carried out, including reference to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product un-packed or a record or returning product that has not been packaged to the storage area. (g) whenever possible, samples of the printed 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 numbers.-- 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 actions 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) status.		

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 processed 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 Schedule, 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		
1.4	Area Grade.-- Area grades must be selected by the manufacturer on the basis of validation runs (e.g. sterile media fills.		
2	**Manufacture of sterile preparations**		
2.1	Manufacturing Operations Classifications are here divided into three categories: (a) Terminally sterilized product.-- 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 how 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, filing 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 C 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 microorganisms 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 dis-infected during operations, masks and gloves shall be changed at least at every working session, and the use of disposable clothing may be followed when 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 fibers 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 single or two-piece 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 fibers or particulate matter. Grade B:-- Headgear shall totally enclose the hair and where appropriate, beard; it shall be tucked into the neck of the suit, 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 fibers 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.		
4.2	Airlock system.-- The entry to the sterile production areas shall be through airlocks for personal and/or for materials. Airlocks 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 of 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 out within the clean area, clean instruments and tools shall be used, and the area shall be cleaned and dis-infected, 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 90C or at temperature validated to keep microbial count of water within the limit.		

SECTION—3			
5.	**Equipment maintenance**		
5.1	Documentation.-- All equipment, including sterilizers, air-filtration systems, and water-treatment systems including still, shall be subject to planned maintenance, validation and monitoring, and its approved use, following maintenance work, shall be documented.		
SECTION—4			
6.1	Procedure.-- The sanitation of clean areas is particularly important, they shall be cleaned frequently and thoroughly in accordance with a written progress 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 microorganisms, 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 containers and shall not be stored for long periods unless sterilized, and partly emptied containers shall not be topped up.		
6.3	Fumigation.-- Fumigation of clean areas may be useful 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 inactivation 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 trials 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 microorganisms, 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.		
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 staring materials.-- Micro-biological contamination (bioburden) of starting materials shall be minimal which shall be monitored before sterilizations, and specifications shall include requirements for microbiological quality when the need for this has been indicated by monitoring.		
7.7	Care against fibres.-- The presence of containers and materials liable to generate fibers shall be minimized in clean areas and avoided completely whole aseptic work is in progress.		
7.8	Care after final cleaning of materials.-- Components, bulk-product containers and equipment shall be handled after the final cleaning process in such a way that they are not recontaminated, and the stage of processing of component, 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 container 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 its 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 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 retaining filter, if possible immediately before the filling process, and when 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 achieved 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 of equipment.		
	SECTION—6		
8	**Sterilization**		
8.1	General.-- Sterilization can be achieved by moist or dry heat, by ethylenoxide or other suitable gaseous sterilizing agent, by filtration with subsequent aseptic filing of sterile final containers, or by irradiation with ionizing radiation but not with ultraviolet radiation unless the process is thoroughly validated each method has its particular applications and limitations, and where possible and practicable heat sterilization is the method of choice.		
8.2	Validation.-- All sterilization processes must be validated and particular attention shall be given when the adopted sterilization method is not in accordance with prarmacopoeial 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 sterilization 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 contaminations from them.		
8.5	Sterilized not sterilized product differentiation.-- There shall be a clean means of differentiating products that have not been sterilized from those that have and each basket, try, 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 whether or not a batch, or sub-batch, has passed through a sterilization process, but they do not give a reliable indication that the lot is, in fact, 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 sterilizer, unless it can be shown that any leaking container would not be approved 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 recorder 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 sterilization period, and there shall be regular leak test 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 containers, 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 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 could 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 microorganism-retaining filter, and where this process of sterilization by dry heat is also intended to remove pyogens, 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 sterilization on 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 does, 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 on 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 even 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 sterilizations, 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 reduce 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 serialization 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 re-action 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 sterilized in the final container can be filtered through a sterile filter of nominal pore size 0.22um or less, or with a least equivalent microorganism-retaining 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 to the potential additional risks of the filtration method as compared with other sterilization processes, a double filter layer or second filtration via a further sterilized microorganism-retaining filter immediately prior to filling may be advisable and the final sterile filtration shall be carried out as close as possible to the filling point.		
14.3	Eliminate fibres.-- Filters that shed fibres shall not be used and the use of asbestos-containing 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 filer 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 same 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 pre-determined 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 worm, and be allowed frequent breaks from inspection, and where other methods of inspection are used, 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 as:-- (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 large-volume 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 necessary.		

SCHEDULE B-III

[See rule 20 (b)]

PARTICULARS TO BE SHOWN IN MANUFACTURING RECORDS

A.	**Substances Parenteral preparation in general:**		Remarks
	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. (All weighing and measurements shall be checked initiated b¥ the competent person in the section). 7. Control reference numbers in 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. Dates 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 packings, 18. Date of release of finished packings 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 weighings 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 filled and number rejected. 15, Reference to Analytical Report numbers stating whether of standard quality or otherwise. 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 packings 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. 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) Identification. (d) Volume in container, (e) Sterility--(/) Bulk sample wherever applicable (ii) container sample. (f) Pyrogen test, wherever applicable. (g) Toxicity test, wherever applicable. (h) Any other teats.(i) Results of assay. 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, 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. 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.		
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.		

Manufacturer's over all rating	**A**	**B**	**C**	**D**
	Good Compliance l	**Fair Compliance**	**Poor Compliance**	**Non-compliance**
Consequences	Needs improvements	Needs active improvements	Needs active improvements and stoppage of production	Stoppage of production and cancellation of License

Recommendations / desired action:

Names and signatures of Inspectors / Panel	Names and signatures of Production / QC Incharge / Plant Manager

Note:

i. The format provides guidance to the Inspectors for reporting, so that no mandatory parameters are left unreported.
ii. Adequate space may be provided for reporting as may be needed, by using soft copy.
iii. Mark "N.A." against the parameter which is Not Applicable, with reasons thereof.
iv. Take in to consideration non compliance to the 'Critical Parameters' which may endanger public health and report accordingly.

Annex-I

Detailed list of Machinery/ Equipment

S. No.	Name	Validation/ Calibration status	Capacity/ shift	Section

Annex-II

Detailed list of Management and technical staff

S.No.	Name	Designation	Qualification	Experience	Section