[1][SCHEDULE M

(*See* Rules 71, 74, 76 and 78)

GOOD MANUFACTURING PRACTICES AND REQUIREMENTS OF PREMISES, PLANT AND EQUIPMENT FOR PHARMACEUTICAL PRODUCTS

Note: *To achieve the objectives listed below, each licensee shall evolve appropriate methodology, systems and procedures which shall be documented and maintained for inspection and reference; and the manufacturing premises shall be used exclusively for production of drugs* [2][*and no other manufacturing activity shall be undertaken therein except in respect of units licensed prior to 11th December, 2001*].

PART 1

GOOD MANUFACTURING PRACTICES FOR PREMISES AND MATERIALS

1 GENERAL REQUIREMENTS:

1.1. *Location and surroundings*.- The factory building(s) for manufacture of drugs shall be so situated and shall have such measures as to avoid risk of contamination from external environment including open sewage, drain, public lavatory or any factory which produce disagreeable or obnoxious odour or fumes, excessive soot, dust, smoke, chemical or biological emissions.

1.2. *Buildings and premises*.- The building(s) used for the factory shall be designed, constructed, adapted and maintained to suit the manufacturing operations so as to permit production of drugs under hygienic conditions. They shall conform to the conditions laid down in the Factories Act, 1948 (63 of 1948).

The premises used for manufacturing, processing, warehousing, packaging, labelling and testing purposes shall be –

(i) compatible with other drug manufacturing operations that may be carried out in the same or adjacent area / section;

(ii) adequately provided with working space to allow orderly and logical placement of equipment, materials and movement of personnel so as to:

(a) avoid the risk of mix-up between different categories of drugs or with raw materials, intermediates and in-process material;

(b) avoid the possibilities of contamination and cross- contamination by providing suitable mechanism;

(iii) designed / constructed / maintained to prevent entry of insects, pests, birds, vermins and rodents. Interior surface (walls, floors and ceilings) shall be smooth and free from cracks, and permit easy cleaning, painting and disinfection;

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1. Subs. by G.S.R. 894(E) , dt. 11.12.2001.- applicable to manufacturers licensed to manufacture drugs, for the period up to 31.12.2003.
2. Subs. by Act 431(E), dt. 30.6.2005.

(iv) air-conditioned, where prescribed for the operations and dosage forms under production. The production and dispensing areas shall be well lighted, effectively ventilated, with air control facilities and may have proper Air Handling Units (wherever applicable) to maintain conditions including temperature and, wherever necessary, humidity, as defined for the relevant product. These conditions shall be appropriate to the category of drugs and nature of the operation. These shall also be suitable to the comforts of the personnel working with protective clothing, products handled, operations undertaken within them in relation to the external environment. These areas shall be regularly monitored for compliance with required specifications;

(v) provided with drainage system, as specified for the various categories of products, which shall be of adequate size and so designed as to prevent back-flow and/or prevent insects and rodents entering the premises. Open channels shall be avoided in manufacturing areas and, where provided, these shall be shallow to facilitate cleaning and disinfection;

(vi) the walls and floors of the areas where manufacture of drugs is carried out shall be free from cracks and open joints to avoid accumulation of dust. These shall be smooth, washable, coved and shall permit easy and effective cleaning and disinfection. The interior surfaces shall not shed particles. A periodical record of cleaning and painting of the premises shall be maintained.

1.3 *Water System.* - There shall be validt. system for treatment of water drawn from own or any other source to render it potable in accordance with standards specified by the Bureau of Indian Standards or Local Municipality, as the case may be, so as to produce Purified Water conforming to Pharmacopoeial specification. Purified Water so produced shall only be used for all the operations except washing and cleaning operations where potable water may be used. Water shall be stored in tanks, which do not adversely affect quality of water and ensure freedom from microbiological growth. The tank shall be cleaned periodically and records maintained by the licensee in this behalf.

1.4. *Disposal of waste.* -

(i) The disposal of sewage and effluents (solid, liquid and gas) from the manufactory shall be in conformity with the requirements of Environment Pollution Control Board.

(ii) All bio-medical waste shall be destroyed as per the provisions of the Bio-Medical Waste (Management and Handling) Rules, 1996.

(iii) Additional precautions shall be taken for the storage and disposal of rejected drugs. Records shall be maintained for all disposal of waste.

(iv) Provisions shall be made for the proper and safe storage of waste materials awaiting disposal. Hazardous, toxic substances and flammable materials shall be stored in suitably designed and segregated, enclosed areas in conformity with Central and State Legislations.

2. ***Warehousing Area****:*

2.1 Adequate areas shall be designed to allow sufficient and orderly warehousing of various categories of materials and products like starting and packaging materials, intermediates, bulk and finished products, products in quarantine, released, rejected, returned or recalled, machine and equipment spare parts and change items.

2.2 Warehousing areas shall be designed and adapted to ensure good storage conditions. They shall be clean, dry and maintained with acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity), these shall be provided, monitored and recorded. Storage areas shall have appropriate house-keeping and rodent, pests and vermin control procedures and records maintained. Proper racks, bins and platforms shall be provided for the storage of materials.

2.3 Receiving and dispatch bays shall protect materials and products from adverse weather conditions.

2.4. Where quarantine status is ensured by warehousing in separate earmarked areas in the same warehouse or store, these areas shall be clearly demarcated. Any system replacing the physical quarantine, shall give equivalent assurance of segregation. Access to these areas shall be restricted to authorized persons.

2.5. There shall be a separate sampling area in the warehousing area for active raw materials and excipients. If sampling is performed in any other area, it shall be conducted in such a way as to prevent contamination, cross-contamination and mix-up.

2.6. Segregation shall be provided for the storage of rejected, recalled or returned materials or products. Such areas, materials or products shall be suitably marked and secured. Access to these areas and materials shall be restricted.

2.7. Highly hazardous, poisonous and explosive materials such as narcotics, psychotropic drugs and substances presenting potential risks of abuse, fire or explosion shall be stored in safe and secure areas. Adequate fire protection measures shall be provided in conformity with the rules of the concerned civic authority.

2.8. Printed packaging materials shall be stored in safe, separate and secure areas.

2.9. Separate dispensing areas for β (Beta) lactum, Sex Hormones and Cytotoxic substances or any such special categories of product shall be provided with proper supply of filtered air and suitable measures for dust control to avoid contamination. Such areas shall be under differential pressure.

2.10. Sampling and dispensing of sterile materials shall be conducted under aseptic conditions conforming to Grade A, which can also be performed in a dedicated area within the manufacturing facility.

2.11. Regular checks shall be made to ensure adequate steps are taken against spillage, breakage and leakage of containers.

2.12. Rodent treatments (Pest control) should be done regularly and at least once in a year and record maintained.

3. *Production area:*

3.1. The production area shall be designed to allow the production preferably in uni-flow and with logical sequence of operations.

3.2. In order to avoid the risk of corss-contamination, separate dedicated and self-contained facilities shall be made available for the production of sensitive pharmaceutical products like penicillin or biological preparations with live micro-organisms. Separate

dedicated facilities shall be provided for the manufacture of contamination causing and potent products such as Beta-Lactum, Sex Hormones and Cytotoxic substances.

3.3. Working and in-process space shall be adequate to permit orderly and logical positioning of equipment and materials and movement of personnel to avoid cross-contamination and to minimize risk of omission or wrong application of any manufacturing and control measures.

3.4. Pipe-work, electrical fittings, ventilation openings and similar service lines shall be designed, fixed and constructed to avoid [1][accumulation of dust]. Service lines shall preferably be identified by colours and the nature of the supply and direction of the flow shall be marked/indicated.

4. ***Ancillary Areas:***

4.1 Rest and refreshment rooms shall be separate from other areas. These areas shall not lead directly to the manufacturing and storage areas.

4.2 Facilities for changing, storing clothes and for washing and toilet purposes shall be easily accessible and adequate for the number of users. Toilets, separate for males and females, shall not be directly connected with production or storage areas. There shall be written instructions for cleaning and disinfection of such areas.

4.3 Maintenance workshops shall be separate and away from production areas. Whenever spares, changed parts and tools are stored in the production area, these shall be kept in dedicated rooms or lockers. Tools and spare parts for use in sterile areas shall be disinfected before these are carried inside the production areas.

4.4. Areas housing animals shall be isolated from other areas. The other requirements regarding animal houses shall be those as prescribed in rule 150-C(3) of the Drugs and Cosmetics Rules, 1945 which shall be adopted for production purposes.

5. ***Quality Control Area.***

5.1. Quality Control Laboratories shall be independent of the production areas. Separate areas shall be provided each for physico-chemical, biological, microbiological or radio-isotope analysis. Separate instrument room with adequate area shall be provided for sensitive and sophisticated instruments employed for analysis.

5.2 Quality Control Laboratories shall be designed appropriately for the operations to be carried out in them. Adequate space shall be provided to avoid mix-ups and cross-contamination. Sufficient and suitable storage space shall be provided for test samples, retained samples, reference standards, reagents and records.

5.3. The design of the laboratory shall take into account the suitability of construction materials and ventilation. Separate air handling units and other requirements shall be provided for biological, microbiological and radioisotopes testing areas. The laboratory shall be provided with regular supply of water of appropriate quality for cleaning and testing purposes.

5.4. Quality Control Laboratory shall be divided into separate sections i.e. for chemical, microbiological and wherever required, biological testing. These shall have adequate area for basic installation and for ancillary purposes. The microbiology section shall have arrangements such as airlocks and laminar air flow work station, wherever considered necessary.

1. Subs. by G.S.R. 431(E), dt. 30.6.2005.

6. *Personnel:*

6.1. The manufacture shall be conducted under the direct supervision of competent technical staff with prescribed qualifications and practical experience in the relevant dosage form and / or active pharmaceutical products.

6.2 The head of the Quality Control Laboratory shall be independent of the manufacturing unit. The testing shall be conducted under the direct supervision of competent technical staff who shall be whole time employees of the licensee.

6.3. Personnel for Quality Assurance and Quality Control operations shall be suitably qualified and experienced.

6.4. Written duties of technical and Quality Control personnel shall be laid and followed strictly.

6.5. Number of personnel employed shall be adequate and in direct proportion to the workload.

6.6. The licensee shall ensure in accordance with a written instruction that all personnel in production area or into Quality Control Laboratories shall receive training appropriate to the duties and responsibility assigned to them. They shall be provided with regular in-service training.

7. *Health, clothing and sanitation of workers*:

7.1 The personnel handling Beta-lactum antibiotics shall be tested for Penicillin sensitivity before employment and those handling sex hormones, cytotoxic substances and other potent drugs shall be periodically examined for adverse effects. These personnel should be moved out of these sections (except in dedicated facilities), by rotation, as a health safeguard.

7.2 Prior to employment, all personnel, shall undergo medical examination including eye examination, and shall be free from Tuberculosis, skin and other communicable or contagious diseases. Thereafter, they should be medically examined periodically, at least once a year. Records shall be maintained thereof. The licensee shall provide the services of a qualified physician for assessing the health status of personnel involved in different activities.

7.3 All persons prior to and during employment shall be trained in practices which ensure personnel hygiene. A high level of personal hygiene shall be observed by all those engaged in the manufacturing processes. Instructions to this effect shall be displayed in change- rooms and other strategic locations.

7.4 No person showing, at any time, apparent illness or open lesions which may adversely affect the quality of products, shall be allowed to handle starting materials, packaging materials, in-process materials, and drug products until his condition is no longer judged to be a risk.

7.5 All employees shall be instructed to report about their illness or abnormal health condition to their immediate supervisor so that appropriate action can be taken.

7.6 Direct contact shall be avoided between the unprotected hands of personnel and raw materials, intermediate or finished, unpacked products.

7.7 All personnel shall wear clean body coverings appropriate to their duties. Before entry into the manufacturing area, there shall be change rooms separate for each sex

with adequate facilities for personal cleanliness such as wash basin with running water, [1][clean towels or hand dryers], soaps, disinfectants, etc. The change rooms shall be provided with cabinets for the storage of personal belongings of the personnel.

7.8 Smoking, eating, drinking, chewing or keeping plants, food, drink and personal medicines shall not be permitted in production, laboratory, storage and other areas where they might adversely influence the product quality.

8. ***Manufacturing Operations and Control:***

8.1 All manufacturing operations shall be carried out under the supervision of technical staff approved by the Licensing Authority. Each critical step in the process relating to the selection, weighing and measuring of raw material addition during various stages shall be performed by trained personnel under the direct personal supervision of approved technical staff.

The contents of all vessels and containers used in manufacture and storage during the various manufacturing stages shall be conspicuously labelled with the name of the product, batch number, batch size and stage of manufacture. Each label should be initialled and dt. by the authorised technical staff.

Products not prepared under aseptic conditions are required to be free from pathogens like *Salmonella, Escherichia coli, Pyocyanea, etc.*

8.2. ***Precautions against mix-up and cross-contamination:***

8.2.1. The licensee shall prevent mix-up and cross-contamination of drug material and drug product (from environmental dust) by proper air-handling system, pressure differential, segregation, status labelling and cleaning. Proper records and Standard Operating Procedures thereof shall be maintained.

8.2.2 The licensee shall ensure processing of sensitive drugs like Beta-Lactum antibiotics, sex hormones and cytotoxic substances in segregated areas or isolated production areas within the building with independent air-handling unit and proper pressure differentials. [1][The effective segregation of these areas shall be validated with adequate records of maintenance and services].

8.2.3 To prevent mix-ups during production stages, material under process shall be conspicuously labelled to demonstrate their status. All equipment used for production shall be labelled with their current status.

8.2.4 Packaging lines shall be independent and adequately segregated. It shall be ensured that all left-overs of the previous packaging operations, including labels, cartons and caps are cleared before the closing hour.

8.2.5 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 and spillages. The line clearance shall be performed according to an approximate check list and recorded.

8.2.6 The correct details of any printing (for example of batch numbers or expiry dates) done separately or in the course of the packaging shall be rechecked at regular intervals. All printing and overprinting shall be authorized in writing.

1. Subs. by G.S.R. 431(E), dt. 30.6.2005.

8.2.7 The manufacturing environment shall be maintained at the required levels of temperature, humidity and cleanliness.

8.2.8 Authorised persons shall ensure change-over into specific uniforms before undertaking any manufacturing operations including packaging.

8.2.9 [1][There shall be segregated secured areas for recalled or rejected material and for such material which are to be reprocessed or recovered.]

9. ***Sanitation in the Manufacturing Premises:***

9.1 The manufacturing premises shall be cleaned and maintained in an orderly manner, so that it is free from accumulated waste, dust, debris and other similar material. A validt. cleaning procedure shall be maintained.

9.2 The manufacturing areas shall not be used for storage of materials, except for the material being processed. It shall not be used as a general thoroughfare.

9.3 A routine sanitation program shall be drawn up and observed, which shall be properly recorded and which shall indicate–

(a) specific areas to be cleaned and cleaning intervals;

(b) cleaning procedure to be followed, including equipment and materials to be used for cleaning; and

(c) personnel assigned to and responsible for the cleaning operation.

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

9.5 Production areas shall be well lit, particularly where visual on-line controls are carried out.

10. ***Raw Materials:***

10.1 The licensee shall keep an inventory of all raw materials to be used at any stage of manufacture of drugs and maintain records as per Schedule U.

10.2 All incoming materials shall be quarantined immediately after receipt or processing. All materials shall be stored under appropriate conditions and in an orderly fashion to permit batch segregation and stock rotation by a 'first in/first expiry' – 'first-out' principle. All incoming materials shall be checked to ensure that the consignment corresponds to the order placed.

10.3 All incoming materials shall be purchased from approved sources under valid purchase vouchers. Wherever possible, raw materials should be purchased directly from the producers.

10.4 Authorized staff appointed by the licensee in this behalf, which may include personnel from the Quality Control Department, shall examine each consignment on receipt and shall check each container for integrity of package and seal. Damaged containers shall be identified, recorded and segregated.

1. Subs. by G.S.R. 431(E), dt. 30.6.2005.

10.5 If a single delivery of material is made up of different batches, each batch shall be considered as a separate batch for sampling, testing and release.

10.6 Raw materials in the storage area shall be appropriately labelled. Labels shall be clearly marked with the following information:

(a) designated name of the product and the internal code reference, where applicable, and analytical reference number;

(b) manufacturer's name, address and batch number;

(c) the status of the contents (e.g. quarantine, under test, released, approved, rejected); and

(d) the manufacturing date, expiry date and re-test date.

10.7 There shall be adequate separate areas for materials "under test", "approved" and "rejected" with arrangements and equipment to allow dry, clean and orderly placement of stored materials and products, wherever necessary, under controlled temperature and humidity.

10.8 Containers from which samples have been drawn shall be identified.

10.9 Only raw materials which have been released by the Quality Control Department and which are within their shelf-life shall be used. It shall be ensured that shelf life of formulation product shall not exceed with that of active raw materials used.

10.10 It shall be ensured that all the containers of raw materials are placed on the raised platforms/racks and not placed directly on the floor.

11. ***Equipment:***

11.1 Equipment shall be located, designed, constructed, adapted and maintained to suit the operations to be carried out. The layout and design of the equipment shall aim to minimise 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. Each equipment shall be provided with a logbook, wherever necessary.

11.2 Balances and other measuring equipment of an appropriate range, accuracy and precision shall be available in the raw material stores, production and in-process control operations and these shall be calibrated and checked on a scheduled basis in accordance with Standard Operating Procedures and records maintained.

11.3 The parts of the production equipment that come into contact with the product shall not be reactive, additive or adsorptive to an extent that would affect the quality of the product.

11.4 To avoid accidental contamination, wherever possible, non-toxic/edible grade lubricants shall be used and the equipment shall be maintained in a way that lubricants do not contaminate the products being produced.

11.5 Defective equipment shall be removed from production and Quality Control areas or appropriately labelled.

12. ***Documentation and Records:–*** Documentation is an essential part of the Quality assurance system and, as such, shall be related to all aspects of Good Manufacturing Practices (GMP). Its aim is to define the specifications for all materials, method of manufacture and control, to ensure that all personnel concerned with manufacture know the information necessary to decide whether or not to release a batch of a drug for sale and to provide an audit trail that shall permit investigation of the history of any suspected defective batch.

12.1 Documents designed, prepared, reviewed and controlled, wherever applicable, shall comply with these rules.

12.2 Documents shall be approved, signed and dt. by appropriate and authorized persons.

12.3 Documents shall specify the title, nature and purpose. They shall be laid out in an orderly fashion and be easy to check. Reproduced documents shall be clear and legible. Documents shall be regularly reviewed and kept up to date. Any alteration made in the entry of a document shall be signed and dt..

12.4 The records shall be made or completed at the time of each operation in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records and associated Standard Operating Procedures (SOP) shall be retained for at least one year after the expiry date of the finished product.

12.5 Data may be recorded by electronic data processing systems or other reliable means, but Master Formulae and detailed operating procedures relating to the system in use shall also be available in a hard copy to facilitate checking of the accuracy of the records. Wherever documentation is handled by electronic data processing methods, authorized persons shall enter or modify data in the computer. There shall be record of changes and deletions. Access shall be restricted by 'passwords' or other means and the result of entry of critical data shall be independently checked. Batch records electronically stored shall be protected by a suitable back-up. During the period of retention, all relevant data shall be readily available.

13. ***Labels and other Printed Materials:–*** Labels are absolutely necessary for identification of the drugs and their use. The printing shall be done in bright colours and in a legible manner. The label shall carry all the prescribed details about the product.

13.1 All containers and equipment shall bear appropriate labels. Different colour coded labels shall be used to indicate the status of a product (for example under test, approved, passed, rejected).

13.2 To avoid chance mix-up of printed packaging materials, product leaflets, relating to different products, shall be stored separately.

13.3 Prior to release, all labels for containers, cartons and boxes and all circulars, inserts and leaflets shall be examined by the Quality Control Department of the licensee.

13.4 Prior to packaging and labelling of a given batch of a drug, it shall be ensured by the licensee that samples are drawn from the bulk and duly tested, approved and released by the quality control personnel.

13.5 Records of receipt of all labelling and packaging materials shall be maintained for each shipment received indicating receipt, control reference numbers and whether accepted or rejected. Unused coded and damaged labels and packaging materials shall be destroyed and recorded.

13.6 The label or accompanying document of reference standards and reference culture shall indicate concentration, lot number, potency, date on which containers was first opened and storage conditions, where appropriate.

14. ***Quality Assurance:–***This is a wide-ranging concept concerning all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that products are of the quality required for their intended use.

14.1 The system of quality assurance appropriate to the manufacture of pharmaceutical products shall ensure that: –

(a) the pharmaceutical products are designed and developed in a way that takes account of the requirements of Good Manufacturing Practices (hereinafter referred as GMP) and other associated codes such as those of Good Laboratory Practices (hereinafter referred as GLP) and Good Clinical Practices (hereinafter referred as GCP);

(b) adequate arrangements are made for manufacture, supply and use of the correct starting and packaging materials.

(c) adequate controls on starting materials, intermediate products and bulk products and other in-process controls, calibrations, and validations are carried out.

(d) the finished product is correctly processed and checked in accordance with established procedures;

(e) the pharmaceutical products are not released for sale or supplied before authorized persons have certified that each production batch has been produced and controlled in accordance with the requirements of the label claim and any other provisions relevant to production, control and release of pharmaceutical products.

15. ***Self Inspection and Quality audit:–*** It may be useful to constitute a self-inspection team supplemented with a quality audit procedure for assessment of all or part of a system with the specific purpose of improving it.

15.1 To evaluate the manufacturer's compliance with GMP in all aspects of production and quality control, concept of self-inspection shall be followed. The manufacturer shall constitute a team of independent, experienced, qualified persons from within or outside the company, who can audit objectively the implementation of methodology and procedures evolved. The procedure for self-inspection shall be documented indicating self-inspection results, evaluation, conclusions and recommended corrective actions with effective follow up program. The recommendations for corrective action shall be adopted.

15.2 The program shall be designed to detect shortcomings in the implementation of Good Manufacturing Practice and to recommend the necessary corrective actions. Self-inspections shall be performed routinely and on specific occasions, like when product recalls or repeated rejections occur or when an inspection by the licensing authorities is announced. The team responsible for self-inspection shall consist of personnel who can evaluate the implementation of Good Manufacturing Practice objectively; all recommendations for corrective action shall be implemented.

15.3 Written instructions for self-inspection shall be drawn up which shall include the following: -

(a) Personnel.
(b) Premises including personnel facilities.
(c) Maintenance of buildings and equipment
(d) Storage of starting materials and finished products.
(e) Equipment.
(f) Production and in-process controls.
(g) Quality control.
(h) Documentation.
(i) Sanitation and hygiene.
(j) Validation and revalidation programmes.
(k) Calibration of instruments or measurement systems.
(l) Recall procedures.
(m) Complaints management.
(n) Labels control.
(o) Results of previous self-inspections and any corrective steps taken.

16. *Quality Control System.* - Quality control shall be concerned with sampling, specifications, testing, documentation, release procedures which ensure that the necessary and relevant tests are actually carried and that the materials are not released for use, nor products released for sale or supply until their quality has been judged to be satisfactory. It is not confined to laboratory operations but shall be involved in all decisions concerning the quality of the product. It shall be ensured that all quality control arrangements are effectively and reliably carried out.The department as a whole shall have other duties such as to establish, evaluate, validate and implement all Quality Control Procedures and methods.

16.1 Every manufacturing establishment shall establish its own quality control laboratory manned by qualified and experienced staff.

16.2 The area of the quality control laboratory may be divided into Chemical, Instrumentation, Microbiological and Biological testing.

16.3 Adequate area having the required storage conditions shall be provided for keeping reference samples. The quality control department shall evaluate, maintain and store reference samples.

16.4 Standard operating procedures shall be available for sampling, inspecting and testing of raw materials, intermediate bulk finished products and packing materials and, wherever necessary, for monitoring environmental conditions.

16.5 There shall be authorized and dt. specifications for all materials, products, reagents and solvents including test of identity, content, purity and quality. These shall include specifications for water, solvents and reagents used in analysis.

16.6 No batch of the product shall be released for sale or supply until it has been certified by the authorized person(s) that it is in accordance with the requirements of the standards laid down.

16.7 Reference/retained samples from each batch of the products manufactured shall be maintained in quantity which is at least twice the quantity of the drug required to conduct all the tests, except sterility and pyrogen/Bacterial Endotoxin Test performed on the active material and the product manufactured. The retained product shall be kept in its final pack or simulated pack for a period of three months after the date of expiry.

16.8 Assessment of records pertaining to finished products shall include all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack. Assessment records should be signed by the in-charge of production and countersigned by the authorised quality control personnel before a product is released for sale or distribution.

16.9 Quality control personnel shall have access to production areas for sampling and investigation, as appropriate.

16.10 The quality control department shall conduct stability studies of the products to ensure and assign their shell life at the prescribed conditions of storage. All records of such studies shall be maintained.

16.11 The in-charge of Quality Assurance shall investigate all product complaints and records thereof shall be maintained.

16.12 All instruments shall be calibrated and testing procedures validt. before these are adopted for routine testing. Periodical calibration of instrument and validation of procedures shall be carried out.

16.13 Each specification for raw materials, intermediates, final products, and packing materials shall be approved and maintained by the Quality Control Department. Periodic revisions of the specifications shall be carried out whenever changes are necessary.

16.14 Pharmacopoeia, reference standards, working standards, references, spectra, other reference materials and technical books, as required, shall be available in the Quality Control Laboratory of the licensee.

17. *Specification*

17.1 *For raw materials and packaging materials.* - They shall include-

(a) the designated name and internal code reference;
(b) reference, if any, to a pharmacopoeial monograph;
(c) qualitative and quantitative requirements with acceptance limits;
(d) name and address of manufacturer or supplier and original manufacturer of the material;
(e) specimen of printed material;
(f) directions for sampling and testing or reference to procedures;
(g) storage conditions; and
(h) maximum period of storage before re-testing.

17.2 *For product containers and closures:–*

17.2.1 All containers and closures intended for use shall comply with the pharmacopoeial requirements. Suitable validt. test methods, sample sizes, specifications, cleaning procedure and sterilization procedure, wherever indicated, shall be strictly followed to ensure that these are not reactive, additive, absorptive, or leach to an extent that significantly affects the quality or purity of the drug. No second hand or used containers and closures shall be used.

17.2.2 Whenever bottles are being used, the written schedule of cleaning shall be laid down and followed. Where bottles are not dried after washing, they should be rinsed with de-ionised water or distilled water, as the case may be.

17.3. *For in-process and bulk products.* - Specifications for in-process material, intermediate and bulk products shall be available. The specifications should be authenticated.

17.4 *For finished products.* - Appropriate specifications for finished products shall include: -

(a) the designated name of the product and the code reference;
(b) the formula or a reference to the formula and the pharmacopoeial reference;
(c) directions for sampling and testing or a reference to procedures;
(d) a description of the dosage form and package details;
(e) the qualitative and quantitative requirements, with the acceptance limits for release;
(f) the storage conditions and precautions, where applicable, and
(g) the shelf-life.

17.5 *For preparation of containers and closures.* - The requirements mentioned in the Schedule do not include requirements of machinery, equipments and premises required for preparation of containers and closures for different dosage forms and categories of drugs. The suitability and adequacy of the machinery, equipment and premises shall be examined taking into consideration the requirements of each licensee in this respect.

18. ***Master Formula Records:***

There shall be Master Formula records relating to all manufacturing procedures for each product and batch size to be manufactured. These shall be prepared and endorsed by the competent technical staff i.e. head of production and quality control. The Master Formula shall include: -

(a) the name of the product together with product reference code relating to its specifications;
(b) the patent or proprietary name of the product along with the generic name, a description of the dosage form, strength, composition of the product and batch size;
(c) name, quantity, and reference number of all the starting materials to be used. Mention shall be made of any substance that may 'disappear' in the course of processing.
(d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.
(e) a statement of the processing location and the principal equipment to be used.
(f) the methods, or reference to the methods, to be used for preparing the critical equipments including cleaning, assembling, calibrating, sterilizing;
(g) detailed stepwise processing instructions and the time taken for each step;
(h) the instructions for in-process control with their limits;
(i) the requirements for storage conditions of the products, including the container, labelling and special storage conditions where applicable;
(j) any special precautions to be observed;
(k) packing details and specimen labels.

19. ***Packing Records:***

There shall be authorised packaging instructions for each product, pack size and type. These shall include or have a reference to the following: -

(a) name of the product;

(b) description of the dosage form, strength and composition;
(c) the pack size expressed in terms of the number of doses, weight or volume of the product in the final container;
(d) 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 of each packaging material.;
(e) reproduction of the relevant printed packaging materials and specimens indicating where batch number and expiry date of the product have been applied;
(f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before the operations begin.
(g) description of the packaging operation, including any significant subsidiary operations and equipment to be used;
(h) details of in-process controls with instructions for sampling and acceptance; and
(i) upon completion of the packing and labelling operation, a reconciliation shall be made between number of labelling and packaging units issued, number of units labelled, packed and excess returned or destroyed. Any significant or unusual discrepancy in the numbers shall be carefully investigated before releasing the final batch.

20. ***Batch Packaging Records:***

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

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

21. ***Batch Processing Records***

21.1 There shall be Batch Processing Record for each product. It shall be based on the relevant parts of the currently approved Master Formula. The method of preparation of such records included in the Master Formula shall be designed to avoid transcription errors.

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

21.3 During processing, the following information shall be recorded at the time each action is taken and the record shall be dt. and signed by the person responsible for the processing operations: -

(a) the name of the product,
(b) the number of the batch being manufactured,
(c) dates and time 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) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed,
(f) any relevant processing operation or event and major equipment used,
(g) a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained,

(h) the amount of product obtained after different and critical stages of manufacture (yield),
(i) comments or explanations for significant deviations from the expected yield limits shall be given,
(j) notes on special problems including details, with signed authorization, for any deviation from the Master Formula,
(k) addition of any recovered or reprocessed material with reference to recovery or reprocessing stages.

22. ***Standard Operating Procedures (SOPs) and Records, regarding:***

22.1 Receipt of materials:

22.1.1 There shall be written Standard Operating Procedures and records for the receipt of each delivery of raw, primary and printed packaging material.

22.1.2 The records of the receipts shall include;

(a) the name of the material on the delivery note and the number of containers;
(b) the date of receipt;
(c) the manufacturer's and/ or supplier's name;
(d) the manufacturer's batch or reference number;
(e) the total quantity, and number of containers, quantity in each container received;
(f) the control reference number assigned after receipt;
(g) any other relevant comment or information.

22.1.3 There shall be written standard operating procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

22.1.4 There shall be Standard Operating Procedures available for each instrument and equipment and these shall be placed in close proximity to the related instrument and equipment.

22.2 ***Sampling:***

22.2.1 There shall be written Standard Operating Procedures for sampling which include the person(s) authorized to take the samples.

22.2.2 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 quantity of samples to be taken,
(e) instructions for any required sub-division or pooling of the samples,
(f) the types of sample container to be used,
(g) any specific precautions to be observed, especially in regard to sampling of sterile and hazardous materials.

22.3. ***Batch Numbering:***

22.3.1 There shall be Standard Operating Procedures describing the details of the batch

(lot) numbering set up with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.

22.3.2 Batch numbering Standard Operating Procedures applied to a processing stage and to the respective packaging stage shall be same or traceable to demonstrate that they belong to one homogenous mix.

22.3.3 Batch number allocation shall be immediately recorded in a logbook or by electronic data processing system. The record shall include date of allocation, product identity and size of batch.

22.4. ***Testing:***

22.4.1 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.

22.5 ***Records of analysis:***

22.5.1 The records shall include the following data:

(a) name of the material or product and the 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 detailed calculations,
(h) a statement of release or rejection, and
(i) signature and date of the designated responsible person.

22.5.2 There shall be written standard operating procedures and the associated records of actions taken for:

(a) equipment assembly and validation
(b) analytical apparatus and calibration,
(c) maintenance, cleaning and sanitation;
(d) personnel matters including qualification, training, clothing, hygiene;
(e) environmental monitoring;
(f) pest control;
(g) complaints;
(h) recalls made; and
(i) returns received.

23. ***Reference Samples****:-*

23.1 Each lot of every active ingredient, in a quantity sufficient to carry out all the tests, except sterility and pyrogens/Bacterial Endotoxin Test, shall be retained for a period of 3 months after the date of expiry of the last batch produced from that active ingredient.

23.2. Samples of finished formulations shall be stored in the same or simulated containers in which the drug has been actually marketed.

24. ***Reprocessing and Recoveries:***

24.1. Where reprocessing is necessary, written procedures shall be established and approved by the Quality Assurance Department that shall specify the conditions and limitations of repeating chemical reactions. Such reprocessing shall be validt..

24.2. If the product batch has to be reprocessed, the procedure shall be authorized and recorded. An investigation shall be carried out into the causes necessitating re- processing and appropriate corrective measures shall be taken for prevention of recurrence. Re-processed batch shall be subjected to stability evaluation.

24.3. Recovery of the product residue may be carried out, if permitted, in the master production and control records by incorporating it in subsequent batches of the product.

25. ***Distribution records:***

25.1. Prior to distribution or dispatch of given batch of a drug, it shall be ensured that the batch has been duly tested, approved and released by the quality control personnel. Pre-dispatch inspection shall be performed on each consignment on a random basis to ensure that only the correct goods are dispatched. Detailed instructions for warehousing and stocking of Large Volume Parenterals, if stocked, shall be in existence and shall be complied with after the batch is released for distribution. Periodic audits of warehousing practices followed at distribution centers shall be carried out and records thereof shall be maintained. Standard Operating Procedures shall be developed for warehousing of products.

25.2. Records for distribution shall be maintained in a manner [1][so as] to facilitate prompt and complete recall of the batch, if and when necessary.

26. ***Validation and process validation:***

26.1. Validation studies shall be an essential part of Good Manufacturing Practices and shall be conducted as per the pre-defined protocols. These shall include validation of processing, testing and cleaning procedures.

26.2. A written report summarizing recorded results and conclusions shall be prepared, documented and maintained.

26.3. Processes and procedures shall be established on the basis of validation study and undergo periodic revalidation to ensure that they remain capable of achieving the intended results. Critical processes shall be validt., prospectively or retrospectively.

26.4. When any new Master Formula or method of preparation is adopted, steps shall be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified shall be demonstrated to yield a product consistently of the required quality.

26.5. Significant changes to the manufacturing process, including any change in equipment or materials that may affect product quality and/or the reproducibility of the process, shall be validt..

1. Subs. by G.S.R. 431(E), dt. 30.6.2005. for " such that finished batch of a drug can be traced to the retail level".

27. ***Product Recalls:***

27.1 A prompt and effective product recall system of defective products shall be devised for timely information of all concerned stockists, wholesalers, suppliers, upto the retail level within the shortest period. The licensee may make use of both print and electronic media in this regard.

27.2. There shall be an established written procedure in the form of Standard Operating Procedure for effective recall of products distributed by the licensee. Recall operations shall be capable of being initiated promptly so as to effectively reach at the level of each distribution channel.

27.3 The distribution records shall be readily made available to the persons designated for recalls.

27.4 The designated person shall record a final report issued, including reconciliation between the delivered and the recovered quantities of the products.

27.5 The effectiveness of the arrangements for recalls shall be evaluated from time to time.

27.6 The recalled products shall be stored separately in a secured segregated area pending final decision on them.

28. ***Complaints and Adverse Reactions:.***

28.1 All complaints thereof concerning product quality shall be carefully reviewed and recorded according to written procedures. Each complaint shall be investigated/evaluated by the designated personnel of the company and records of investigation and remedial action taken thereof shall be maintained.

28.2. Reports of serious adverse drug reactions resulting from the use of a drug along with comments and documents shall be forthwith reported to the concerned licensing authority.

28.3 There shall be written procedures describing the action to be taken, recall to be made of the defective product.

29. ***Site Master File.*** **–**The licensee shall prepare a succinct document in the form of 'Site Master File' containing specific and factual Good Manufacturing Practices about the production and/or control of pharmaceutical manufacturing preparations carried out at the licensed premises. It shall contain the following: -

29.1 ***General information:***

(a) brief information of the firm;
(b) pharmaceutical manufacturing activities as permitted by the licensing authority;
(c) other manufacturing activities, if any, carried out on the premises;
(d) type of products licensed for manufacture with flow charts mentioning procedure and process flow;
(e) number of employees engaged in the production, quality control, storage and distribution;
(f) use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;
(g) short description of the Quality Management System of the firm; and
(h) products details registered with foreign countries.

29.2 ***Personnel:***

(a) organisational chart showing the arrangement for quality assurance including production and quality control;
(b) qualification, experience and responsibilities of key personnel;
(c) outline for arrangements for basic and in-service training and how the records are maintained;
(d) health requirements for personnel engaged in production; and
(e) personnel hygiene requirements, including clothing.

29.3 ***Premises:***

(a) simple plan or description of manufacturing areas drawn to scale;
(b) nature of construction and fixtures/fittings;
(c) brief description of ventilation systems. More details should be given for critical areas with potential risk of airborne contamination (schematic drawing of systems). Classification of the rooms used for the manufacture of sterile products should be mentioned;
(d) special areas for the handling of the highly toxic, hazardous and sensitizing materials;
(e) brief description of water system (schematic drawings of systems), including sanitation;
(f) description of planned preventive maintenance programs for premises and of the recording system.

29.4 ***Equipment:***

(a) brief description of major equipment used in production and Quality Control Laboratories (a list of equipment required);
(b) description of planned preventive maintenance programs for equipment and of the recording system; and
(c) qualification and calibration including the recording systems and arrangements for computerized systems validation.

29.5 ***Sanitation:***

(a) availability of written specifications and procedures for cleaning manufacturing areas and equipment.

29.6 ***Documentation. -***

(a) arrangements for the preparation, revision and distribution of;
(b) necessary documentation for the manufacture;
(c) any other documentation related to product quality that is not mentioned elsewhere (e.g. microbiological controls about air and water).

29.7 ***Production:.***

(a) brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters;
(b) arrangements for the handling of starting materials, packaging materials, bulk and

finished products, including sampling, quarantine, release and storage;

(c) arrangements for the handling of rejected materials and products;

(d) brief description of general policy for process validation.

29.8 ***Quality Control:***

(a) description of the quality control system and of the activities of the Quality Control Department. Procedures for the release of the finished products.

29.9 ***Loan licence manufacture and licensee*:**

(a) description of the way in which compliance of Good Manufacturing Practices by the loan licensee shall be assessed.

29.10 ***Distribution, complaints and product recall:***

(a) arrangements and recording system for distribution;

(b) arrangements for the handling of complaints and product recalls.

29.11 *Self inspection. -*

(a) short description of the self-inspection system indicating whether an outside, independent and experienced external expert was involved in evaluating the manufacturer's compliance with Good manufacturing Practices in all aspects of production.

29.12 ***Export of drugs. -***

(a) products exported to different countries;

(b) complaints and product recall, if any.

PART IA

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF STERILE PRODUCTS, PARENTERAL PREPARATIONS (SMALL VOLUME INJECTABLES AND LARGE VOLUME PARENTERALS) AND STERILE OPHTHALMIC PREPARATIONS.

Note. - The general requirements as given in Part 1 of this Schedule relating to Requirements of Good Manufacturing Practices for Premises and Materials for pharmaceutical products shall be complied with, *mutatis mutandis*, for the manufacture of sterile products, Parenteral preparations (Small Volume Injectables and Large Volume Parenterals) and Sterile Ophthalmic Preparations. In addition to these requirements, the following specific requirements shall also be followed, namely: -

1. ***General :***

Sterile products, being very critical and sensitive in nature, a very high degree of precautions, prevention and preparations are needed. Dampness, dirt and darkness are to be avoided to ensure aseptic conditions in all areas. There shall be strict compliance in the prescribed standards especially in the matter of supply of water, air, active materials and in the maintenance of hygienic environment.

2. ***Buildings and Civil Works:***

2.1 The buildings shall be built on proper foundation with standardized materials to avoid cracks in critical areas like aseptic solution preparation, filling and sealing rooms.

2.2 Location of services like water, steam, gases etc. shall be such that their servicing or repair shall not pose any threat to the integrity of the facility. Water lines shall not pose any threat of leakage to aseptic area.

2.3. The manufacturing areas shall be clearly separated into support areas (e.g. washing and component preparation areas, storage areas etc.), preparation areas (e.g. bulk manufacturing area, non-aseptic blending areas etc.) change areas and aseptic areas. Operations like removal of outer cardboard wrappings of primary packaging materials shall be done in the de-cartoning areas which are segregated from the washing areas. Wooden pallets, fiber board drums, cardboard and other particle shedding materials shall not be taken inside the preparation areas.

2.4. In aseptic areas –

(a) walls, floors and ceiling should be impervious, non-shedding, non-flaking and non-cracking. Flooring should be unbroken and provided with a cove both at the junction between the wall and the floor as well as the wall and the ceiling.

(b) walls shall be flat, and ledges and recesses shall be avoided. Wherever other surfaces join the wall (e,g, sterilizers, electric sockets, gas points etc.) these shall flush the walls. Walls shall be provided with a cove at the joint between the ceiling and the floor;

(c) ceiling shall be solid and joints shall be sealed. Light-fittings and air-grills shall flush with the walls and not hanging from the ceiling, so as to prevent contamination;

(d) there shall be no sinks and drains in Grade A and Grade B areas;

(e) doors shall be made of non-shedding material. These may be made preferably of Aluminium or Steel material. Wooden doors shall not be used. Doors shall open towards the higher-pressure area so that they close automatically due to air pressure;

(f) Windows shall be made of similar material as the doors, preferably with double panel and shall be flush with the walls. If fire escapes are to be provided, these shall be suitably fastened to the walls without any gaps;

(g) The furniture used shall be smooth, washable and made of stainless steel or any other appropriate material other than wood.

2.5. The manufacturing and support areas shall have the same quality of civil structure described above for aseptic areas, except the environmental standards which may vary in the critical areas.

2.6 Change rooms with entrance in the form of air-locks shall be provided before entry into the sterile product manufacturing areas and then to the aseptic area. Separate exit space from the aseptic areas is advisable. Change rooms to the aseptic areas shall be clearly demarcated into ‘black’. ‘grey’, and ‘white rooms’ with different levels of activity and air cleanliness. The ‘black’ change room shall be provided with a hand-washing sink. The sink

and its drain in the un-classified (first) change rooms may be kept clean all the time. The specially designed drain shall be periodically monitored to avoid presence of pathogenic micro-organisms. Change room doors shall not be opened simultaneously. An appropriate inter-locking system and a visual and/or audible warning system may be installed to prevent the opening of more than one door at a time.

2.7. For communication between aseptic areas and non-aseptic areas, intercom telephones or speak-phones shall be used. These shall be minimum in number.

2.8 Material transfer between aseptic areas and outside shall be through suitable airlocks or pass-boxes. Doors of such airlocks and pass-boxes shall have suitable interlocking arrangements.

2.9. Personal welfare areas like rest rooms, tea room, canteen and toilets shall be outside and separated from the sterile product manufacturing area.

2.10 Animal houses shall be away from the sterile product manufacturing area and shall not share a common entrance or air handling system with the manufacturing area.

3. ***Air Handling System (Central Air-Conditioning):***

3.1 Air Handling Units for sterile product manufacturing areas shall be different from those for other areas. Critical areas, such as the aseptic filling area, sterilized components unloading area and change room conforming to Grades B, C and D respectively shall have separate air handling units. The filter configuration in the air handling system shall be suitably designed to achieve the Grade of air as given in Table1. Typical operational activities for clean areas are highlighted in Table II and Table III.

3.2 For products which are filled aseptically, the filling room shall meet Grade B conditions at rest unmanned. This condition shall also be obtained within a period of about 30 minutes of the personnel leaving the room after completion of operations.

3.3. The filling operations shall take place under Grade A conditions which shall be demonstrated under working of simulated conditions which shall be achieved by providing laminar air flow work stations with suitable HEPA filters or isolator technology.

3.4. For products, which are terminally sterilized, the filling room shall meet Grade C conditions at rest. This condition shall be obtainable within a period of about 30 minutes of the personnel leaving the room after completion of operations.

3.5. Manufacturing and component preparation areas shall meet Grade C conditions.

3.6. After completion of preparation, washed components and vessels shall be protected with [1][Grade D background and should be handled in such a way that they are not recontaminated].

3.7. The minimum air changes for Grade B and Grade C areas shall not be less than 20 air changes per hour in a room with good air flow pattern and appropriate HEPA filters. For Grade A laminar air flow work stations, the air flow rate shall be 0.3 meter per second ± 20% (for vertical flows) and 0.45 meter per second ± 20% (for horizontal flows).

3.8. Differential pressure between areas of different environmental standards shall be at least 15 Pascal (0.06 inches or 1.5 mm water gauge). Suitable manometers or gauges shall be installed to measure and verify pressure differential.

1. Subs. by G.S.R. 431(E), dt. 30.6.2005

3.9 The final change room shall have the same class of air as specified for the aseptic area. The pressure differentials in the change rooms shall be in the descending order from 'white' to 'black'.

3.10 Unless there are product specific requirements, temperature and humidity in the aseptic areas [1][shall be 27 ± 2 degree centigrade and relative humidity 55% ± 5, respectively].

[1][**TABLE I**

AIR BORNE PARTICULATE CLASSIFICATION FOR MANUFACTURE OF STERILE PRODUCTS

Grade	**Maximum number of permitted particles per cubic metre equal t to or above**			
	At rest (b)		In operation (a)	
	0.5µm	5µm	0.5µm	5µm
A	3500	0	3500	0
B (a)	3500	0	3,50,000	2,000
C (a)	350,000	2,000	35,00,000	20,000
D (a)	35,00,000	20,000	Not defined (c)	Not defined (c)]

Notes :

(a) In order to reach the B, C and D air grades, the number of air changes shall be related to the size of the room and the equipment and personnel present in the room. The air system shall be provided with the appropriate filters such as HEPA for Grades A, B and C. The maximum permitted number of particles in the "at rest" condition shall approximately be as under:

[1][*Grade A and B corresponds with class 100 or M 3.5 or class 5*]*; Grade C with Class 10,000 or M 5.5 or ISO Class 7; Grade D with Class 1,00,000 or M 6.5 or ISO Class 8.*

(b) *The requirement and limit for the area shall depend on the nature of the operation carried out.*

(c) *Type of operations to be carried out in the various grades are given in Table II and Table III as under:*

TABLE II

TYPES OF OPERATIONS TO BE CARRIED OUT IN THE VARIOUS GRADES FOR ASEPTIC PREPARATIONS

Grade	Types of operations for aseptic preparations
A	Aseptic preparation and filling
B	Background room conditions for activities requiring Grade A
C	Preparation of solution to be filtered
D	Handling of components after washing

1. Subs. by G.S.R. 431(E), dt. 30.6.2005.

TABLE III

TYPES OF OPERATIONS TO BE CARRIED OUT IN THE VARIOUS GRADES FOR TERMINALLY STERILIZED PRODUCTS

Grade	Types of operations for terminally sterilized products.
A	Filling of products, which are usually at risk.
C	Placement of filling and sealing machines, preparation of solutions when [1][unusually at risk]. Filling of product when unusually at risk.
D	Moulding, blowing (pre-forming) operations of plastic containers, preparations of solutions and components for subsequent filling.

4. ***Environmental Monitoring:***

4.1 All environmental parameters listed under para 3.1 to 3.10 shall be verified and established at the time of installation and thereafter monitored at periodic intervals. The recommended frequencies of periodic monitoring shall be as follows :-

(a) Particulate monitoring in air – 6 Monthly.
(b) HEPA filter integrity testing (smoke testing) – Yearly
(c) Air change rates – 6 Monthly.
(d) Air pressure differentials – Daily.
(e) Temperature and humidity – Daily
(f) Microbiological monitoring by settle plates and/or swabs in aseptic areas– Daily, and at decreased frequency in other areas.

`***Note****:* The above frequencies of monitoring shall be changed as per the requirements and load in individual cases.

4.2 There shall be a written environmental monitoring program and microbiological results shall be recorded. Recommended limits for microbiological monitoring of clean areas "in operation" are as given in the table below:

TABLE

RECOMMENDED LIMITS FOR MICROBIOLOGICAL MONITORING OF CLEAN AREAS " IN OPERATION"

Grade	Air sample Cfu/m^2	Settle plates (dia. 90mm. Cfu/2 hrs.	Contact plates (dia. 55mm) cfu per plate	Glove points (five fingers) cfu per glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	--
D	500	100	50	--

Notes:

(a) These are average values.
(b) Individual settle plates may be exposed for not less than two hours in Grade B, C and D areas and for not less than thirty minutes in Grade A area.

1. Subs. by G.S.R. 431(E), dt. 30.6.2005.

4.3 Appropriate action shall be taken immediately if the result of particulate and microbiological monitoring indicates that the counts exceed the limits. The Standard Operating Procedures shall contain corrective action. After major engineering modification to the HVAC system of any area, all monitoring shall be re-performed before production commences.

5. *Garments.*

5.1 This section covers garments required for use by personnel working only in aseptic area. Outdoor clothing shall not be brought into the sterile areas.

5,2 The garments shall be made of non-shedding and tight weave material. Cotton garments shall not be used. The garments shall shed virtually no fibres or particulate matter.

5.3 The clothing and its quality shall be adopted to the process and the work place and worn in such a way as to protect the product from contamination. Garments shall be single piece with fastenings at cuffs, neck and at legs to ensure close fit. Trouser legs shall be tucked inside the cover boots. Suitable design of garments shall either include a hood (head-cover) or a separate hood which can be tucked inside the over-all. Pockets, pleats and belts shall be avoided in garments. Zips (if any) shall be of plastic material. Garments with damaged zips shall not be used.

5.4. Only clean, sterilized and protective garments shall be used at each work session where aseptic filtration and filling operations are undertaken and at each work shift for products intended to be sterilized, post-filling. The mask and gloves shall be changed at every work session in both instances.

5.5 Gloves shall be made of latex or other suitable plastic materials and shall be powder-free. These shall be long enough to cover wrists completely and allow the over-all cuff to be tucked in.

5.6. The footwear shall be of suitable plastic or rubber material and shall be daily cleaned with a bactericide.

5.7. Safety goggles or numbered glasses with side extension shall be used inside aseptic areas. These shall be sanitized by a suitable method.

5.8. Garment changing procedures shall be documented and operators trained in this respect. A full size mirror shall be provided in the final change room for the operator to verify that he is appropriately attired in the garments. Periodic inspection of the garments shall be done by responsible staff.

6. *Sanitation:*

6.1. There shall be written procedures for the sanitation of sterile processing facilities. Employees carrying out sanitation of aseptic areas shall be trained specifically for this purpose.

6.2. Different sanitizing agent shall be used in rotation and the concentrations of the same shall be as per the recommendations of the manufacturer. Records of rotational use of sanitizing agents shall be maintained.

6.3. Distilled water freshly collected directly from the distilled water plant or water maintained above 70 degree centigrade from the re-circulation loop shall be used for dilution of disinfectants. Alternatively, distilled water sterilized by autoclaving or membrane filtration shall be used. The dilution shall be carried out in the ‘white’ change room.

6.4. [1][Where alcohol or isopropyl alcohol is used for dilution of disinfectants for use as hand sprays, the preparation of the same shall be done in the bulk preparation area in grade C.]

6.5. Diluted disinfectants shall bear the label 'use before', based on microbiological establishment of the germicidal properties. The solutions shall be adequately labelled and documents maintained.

6.6. Formaldehyde or any other equally effective fumigant is recommended for the fumigation of aseptic areas or after major civil modifications. There shall be Standard Operating Procedures for this purpose. Its use for routine purpose shall be discouraged and an equally effective surface cleaning regime shall be followed.

6.7. Cleaning of sterile processing facilities shall be undertaken with air suction devices or with non-linting sponges or clothes.

6.8. Air particulate quality shall be evaluated on a regular basis and record maintained.

7. *Equipment:*

7.1 The special equipment required for manufacturing sterile products includes component washing machines, steam sterilizers, dry heat sterilizers, membrane filter assemblies, manufacturing vessels, blenders, liquid filling machines, powder filling machines, sealing and labelling machines, vacuum testing chambers, inspection machines, lyophilisers, pressure vessels etc. Suitable and fully integrated washing sterilizing filling lines may be provided, depending upon the type and volume of activity.

7.2. Unit-sterilizers shall be double-ended with suitable inter-locking arrangements between the doors. The effectiveness of the sterilization process shall be established initially by biological inactivation studies using microbial spore indicators and then at least once a year by carrying out thermal mapping of the chamber. Various sterilization parameters shall be established based on these studies and documented. For membrane filters used for filtration, appropriate filter integrity tests that ensure sterilization shall be carried out before and after filtration.

7.3. Filling machines shall be challenged initially and then at periodic intervals by simulation trials including sterile media fill. Standard Operating Procedures and acceptance criteria for media fills shall be established, justified and documented. Special simulation trial procedures shall be developed, validt. and documented for special products like ophthalmic ointments.

7.4. The construction material used for the parts which are in direct contact with products and the manufacturing vessels may be stainless steel 316 or Boro-silicate glass (if glass containers) and the tubing shall be capable of being washed and autoclaved.

7.5 On procurement, installation qualification of each of the equipment shall be done by engineers with the support of production and quality assurance personnel. Equipment for critical processes like aseptic filling and sterilizers shall be suitably validt. according to a written program before putting them to use.

7.6. Standard Operating Procedures shall be available for each equipment for its calibration and operation and cleaning. Gauges and other measuring devices attached to equipment shall be calibrated at suitable intervals against a written program. Calibration status of equipment gauges shall be adequately documented and displayed.

1. Subs. by G.S.R. 431(E), dt. 30.6.2005.

8. *Water and Steam Systems:*

8.1. Potable water meeting microbiological specification of not more than 500 cfu/ml and indicating absence of individual pathogenic micro-organisms. *Escherichia coli, Salmonella, Staphylococcus aureus and Pseudomonas aeruginosa* per 100 ml sample shall be used for the preparation of purified water.

8.2 Purified water prepared by de-mineralization shall meet the microbiological specification of not more than 100 cfu per ml and indicate absence of pathogenic micro-organisms in 100 ml. Purified water shall also meet IP specification for chemical quality. Purified water shall be used for hand washing in change rooms. Containers, closures and machine parts may be washed with potable water followed by suitably filtered purified water. Purified water shall be stored in stainless steel tanks or plastic tanks.

8.3. Water for Injection (hereinafter as WFI) shall be prepared from potable water or purified water meeting the above specifications by distillation. Water for Injection shall meet microbiological specification of not more than 10 cfu per 100 ml. WFI shall also meet IP specification for Water for Injection and shall have an endotoxin level of not more than 0.25 EU/Ml. Bulk solutions of liquid parenterals shall be made in WFI. Final rinse of product containers and machine parts shall be done with WFI. Disinfectant solutions for use in aseptic areas shall be prepared in WFI.

8.4. Water for Injection for the manufacture of liquid injectables shall be freshly collected from the distillation plant or from a storage or circulation loop where the water has been kept at above 70 degree centigrade. At the point of collection, water may be cooled using suitable heat exchanger.

8.5 Water for non-injectable sterile products like eye drops shall meet IP specifications for purified water. In addition, microbiologial specification of not more than 10 cfu per 100 ml and absence of *Pseudomonas aeruginosa* and *Enterobacter coli* in 100 ml shall also be met.

8.6. Water for Injection shall be stored in steam jacketed stainless steel tanks of suitable size and the tanks shall have hydrophobic bacterial retention with 0.22 μ vent filters. The filters shall be suitably sterilized at periodic intervals. The distribution lines for purified water and distilled water shall be of stainless steel 316 construction and shall not shed particles.

8.7. There shall be a written procedure and program for the sanitation of different water systems including storage tanks, distribution lines, pumps and other related equipment. Records of sanitation shall be maintained.

8.8. There shall be written microbiological monitoring program for different types of water. The results shall justify the frequency of sampling and testing. Investigation shall be carried out and corrective action taken in case of deviation from prescribed limits.

[1][8.9 Steam coming in contact with the product, primary containers and other product contact surfaces shall be sterile and pyrogen free.]

9. *Manufacturing Process:*

9.1. Manufacture of sterile products shall be carried out only in areas under defined conditions.

1. Omitted by G.S.R. 431(E), dt. 30.6.2005.

9.2. Bulk raw materials shall be monitored for bio-burden periodically. Bio-burden of bulk solution prior to membrane filtration shall be monitored periodically and a limit of not more than 100 cfu per ml is recommended.

9.3 The time between the start of the preparation of the solution and its sterilization or filtration through a micro-organism retaining filter shall be minimized. There shall be a set maximum permissible time for each product that takes into account its composition and method of storage mentioned in the Master formula record.

9.4. Gases coming in contact with the sterile product shall be filtered through two 0.22 µ hydrophobic filters connected in-series. These filters shall be tested for integrity. Gas cylinders shall not be taken inside aseptic areas.

9.5. Washed containers shall be sterilized immediately before use. Sterilized containers, if not used within an established time, shall be rinsed with distilled or filtered purified water and re-sterilized.

9.6. Each lot of finished product shall be filled in one continuous operation. In each case, where one batch is filled in using more than one operation, each lot shall be tested separately for sterility and held separately till sterility test results are known.

9.7. Special care shall be exercised while filling products in powder form so as not to contaminate the environment during transfer of powder to filling machine-hopper.

10. ***Form-Fill-Seal Technology or Blow, Fill-Seal Technology****:*

10.1 Form-Fill-Seal units are specially built automated machines in which through one continuous operation, containers are formed from thermoplastic granules, filled and then sealed. Blow, fill-seal units are machines in which containers are moulded / blown (pre-formed) in separate clean rooms, by non-continuous operations.

Note:
(i) These shall be installed in at least Grade C environment.
(ii) These shall comply with the limits as recommended in Table at Item 4.2.

10.2. Form-Fill-Seal/Blow, Fill-Seal machines used for the manufacture of products for terminal sterilization shall be installed in at least Grade C environment and the filling zone within the machine shall fulfil Grade A requirements.

10.3. *Terminally sterilized products.*–

10.3.1. Preparation of primary packaging material such as glass bottles, ampoules and rubber stoppers shall be done in at least Grade D environment. Where there is unusual risk to the product from microbial contamination, the above operation shall be done in Grade C environment. All the processes used for component preparation shall be validt..

10.3.2. Filling of products requiring terminal sterilization shall be done under Grade A environment with a Grade C background.

10.4 Preparation of solutions, which are to be sterilized by filtration, shall be done in Grade C environment, and if not to be filtered, the preparation of materials and products shall be in a Grade A environment with Grade B in background.

10.5 *Filtration (Membrane).-*

(i) Solutions for Large Volume Parenterals shall be filtered through a non-fibre releasing, sterilizing grade cartridge/membrane filter of nominal pore size of 0.22 µ for aseptic filling whereas 0.45 µ porosity shall be used for terminally sterilized products.

(ii) A second filtration using another 0.22 µ sterilizing grade cartridge / membrane filter shall be performed immediately prior to filling. Process specifications shall indicate the maximum time during which a filtration system may be used with a view to precluding microbial build-up to levels that may affect the microbiological quality of the Large Volume Parenterals.

(iii) The integrity of the sterilized filter shall be verified and confirmed immediately after use by an appropriate method such as Bubble Point, Diffusive Flow or Pressure Hold Test.

10.6 *Sterilization (Autoclaving).–*

10.6.1. 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 pattern to be processed, shall be demonstrated by physical measurements and by biological indicators, where appropriate.

10.6.2 All the sterilization process shall be appropriately validt.. The validity of the process shall be verified at regular intervals, but at least annually. Whenever significant modifications have been made to the equipment and product, records shall be maintained thereof.

10.6.3 The sterilizer shall be double ended to prevent mix-ups.

10.6.4 Periodic bio-burden monitoring of products before terminal sterilization shall be carried out and controlled to limits specified for the product in the Master Formula.

10.6.5 The use of biological indicators shall be considered as an additional method of monitoring the sterilization. These shall be stored and used according to the manufacturer's instructions. Their quality shall be checked by positive controls. If biological indicators used, strict precautions shall be taken to avoid transferring microbial contamination from them.

10.6.6 There shall be clear means of differentiating ' sterilized' and 'un-sterilized' products. Each basket, tray or other carrier of products or components shall be clearly labelled with the name of the material, its batch number, and sterilization status. Indicators shall be used, where appropriate, to indicate whether a batch (or sub-batch) has passed through the sterilization process.

10.6.7 Sterilization records shall be available for each sterilization-run and may also include thermographs and sterilization monitoring strips. They shall be maintained as part of the batch release procedure.

10.7. *Sterilization (By dry heat).–*

10.7.1 Each heat sterilization cycle shall be recorded on a time/temperature chart of a suitable size by appropriate equipment of the required accuracy and precision. The position of temperature probes used for controlling and/or recording shall be determined during the validation and, where applicable, shall also be checked against a second independent temperature probe located in the same position. The chart shall form a part of the

batch record. Container mapping may also be carried out in the case of Large Volume Parenterals.

10.7.2 Chemical or biological indicators may also be used, but shall not take the place of physical validation.

10.7.3. Sufficient time shall be allowed for the load to reach the required temperature before measurement of sterilization time commences. This time shall be separately determined for each type of load to be processed.

10.7.4. After the high temperature phase of a heat sterilization cycle, precautions shall be taken against contamination of sterilized load during cooling. 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 approved for use. Air inlet and outlets shall be provided with bacterial retaining filters.

10.7.5. 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. Air inlets and outlets should be provided with micro-organism retaining filters. 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 process.

10.8. *Sterilization (By Moist Heat)*.-

10.8.1 Both the temperature and pressure shall be used to monitor the process. Control instrumentation shall normally be independent of monitoring instrumentation and recording charts. Where automated control and monitoring systems are used for these applications, these shall be validt. to ensure that critical process requirements are met. System and cycle faults shall be registered by the system and observed by the operator. The reading of the independent temperature indicator shall be routinely checked against the chart-recorder during the sterilization period. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the temperature at this position throughout the sterilization period. There shall be frequent leak tests done on the chamber during the vacuum phase of the cycle.

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

10.8.3. No Large Volume Parenteral shall be subjected to steam sterilization cycle until it has been filled and sealed.

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

10.9. *Completion/finalisation of sterile products*–

10.9.1. All unit operations and processes in the manufacture of a batch shall have a minimum time specified and the shortest validt. time shall be used from the start of a batch to its ultimate release for distribution.

10.9.2. Containers shall be closed by appropriately validt. methods. Containers closed by fusion e.g. glass or plastic ampoules shall be subjected to 100% integrity testing. Samples of other containers shall be checked for integrity according to appropriate procedures.

10.9.3 Containers sealed under vacuum shall be tested for required vacuum conditions.

10.9.4 Filled containers of parenteral products shall be inspected individually for extraneous contamination or other defects. When inspection is done visually, it shall be done under suitably controlled conditions of illumination and background. Operators doing the inspection shall pass regular eye-sight checks with spectacles, if worn, and be allowed frequent rest from inspection. Where other methods of inspection are used, the process shall be validt. and the performance of the equipment checked at suitable intervals. Results shall be recorded.

11. ***Product Containers and Closures.*** **–**

11.1 All containers and closures intended for use shall comply with the pharmacopoeial and other specified requirements. Suitable samples sizes, specifications, test methods, cleaning procedures and sterilization procedures, shall be used to assure that containers, closures and other component parts of drug packages are suitable and are not reactive, additive, adsorptive or leachable or presents the risk of toxicity to an extent that significantly affects the quality or purity of the drug. No second hand or used containers and closures shall be used.

11.2 Plastic granules shall also comply with the pharmacopoeial requirements including physio-chemical and biological tests.

11.3. All containers and closures shall be rinsed prior to sterilization with Water for Injection according to written procedure.

11.4. The design of closures, containers and stoppers shall be such as to make cleaning, easy and also to make airtight seal when fitted to the bottles.

11.5 It shall be ensured that containers and closures chosen for a particular product are such that when coming into contact they are not absorbed into the product and they do not affect the product adversely. The closures and stoppers should be of such quality substances as not to affect the quality of the product and avoid the risk of toxicity.

11.6. Whenever glass bottles are used, the written schedule of cleaning shall be laid down and followed. Where bottles are not dried after washing, these shall be finally rinsed with distilled water or pyrogen free water, as the case may be, according to written procedure.

11.7. Individual containers of parenteral preparations, ophthalmic preparations shall be examined against black/white background fitted with diffused light after filling so as to ensure freedom from foreign matters.

11.8 *Glass Bottles.* **–**

11.8.1 Shape and design of the glass bottle shall be rational and standardized. Glass bottles made of USP Type-I and USP Type-II glass shall only be used. Glass bottles shall not be reused. Before use, USP Type-II bottles shall be validt. for the absence of particulate matter generated over a period of the shelf -life of the product and shall be

regularly monitored after the production, following statistical sampling methods. USP Type-III glass containers may be used for non-parenteral sterile products such as Otic Solutions.

11.9. *Plastic Containers.* –

11.9.1 Pre-formed plastic containers intended to be used for packing of Large Volume Parenteral shall be moulded in-house by one-continuous operation through an automatic machine.

11.9.2. Blowing, filling and sealing (plugging) operation shall be conducted in room(s) conforming to requirements as mentioned in Table III of Item 3.10. Entry to the area where such operations are undertaken, shall be through a series of airlocks. Blowers shall have an air supply which is filtered through 0.22µ filters. Removal of runners and plugging operations shall be conducted under a laminar airflow workstation.

11.10 *Rubber Stoppers.* –

11.10.1 The rubber stoppers used for Large Volume Parenterals shall comply with specifications prescribed in the current edition of the Indian Pharmacopoeia.

12. *Documentation:*

12.1 The manufacturing records relating to manufacture of sterile products shall indicate the following details:-

(1) Serial number of the Batch Manufacturing Record.
(2) Name of the product
(3) Reference to Master Formula Record.
(4) Batch/Lot number
(5) Batch/Lot size.
(6) Date of commencement of manufacture and date of completion of manufacture.
(7) Date of manufacture and assigned date of expiry.
(8) Date of each step in manufacturing.
(9) Names of all ingredients with the grade given by the quality control department.
(10) Quality of all ingredients.
(11) Control reference numbers for all ingredients.
(12) Time and duration of blending, mixing, etc. whenever applicable.
(13) pH of solution whenever applicable.
(14) Filter integrity testing records
(15) Temperature and humidity records whenever applicable
(16) Records of plate-counts whenever applicable.
(17) Results of pyrogen and/or bacterial endotoxin & toxicity.
(18) Records of weight or volume of drug filled in containers.
(19) Bulk sterility in case of aseptically filled products.
(20) Leak test records.
(21) Inspection records.
(22) Sterilization records including autoclave leakage test records, load details, date, duration, temperature, pressure, etc.
(23) Container washing records.
(24) Total number of containers filled.
(25) Total numbers of containers rejected at each stage
(26) Theoretical yield, permissible yield, actual yield and variation thereof.
(27) Clarification for variation in yield beyond permissible yield.
(28) Reference numbers of relevant analytical reports.
(29) Details of reprocessing, if any.

(30) Name of all operators carrying out different activities.
(31) Environmental monitoring records.
(32) Specimens of printed packaging materials.
(33) Records of destruction of rejected containers and printed packaging materials.
(34) Signature of competent technical staff responsible for manufacture and testing.

***Note*:** (*1) Products shall be released only after complete filling and testing.*

(2) Result of the tests relating to sterility, pyrogens, and Bacterial endotoxins shall be maintained in the analytical records.

(3) Validation details and simulation trial records shall be maintained separately,

(4) Records of environmental monitoring like temperature, humidity, microbilogical data, etc. shall be maintained. Records of periodic servicing of HEPA filters, sterilizers and other periodic maintenance of facilities and equipment carried out also be maintained.

(5) Separate facilities shall be provided for filling-cum-sealing of Small Volume Injectables and Large Volume Parenterals.

(6) It is advisable to provide separate facilities for manufacture of Large Volume Parenterals in glass containers and / or plastic containers.

(7) For manufacture of Large Volume Parenterals in plastic containers, it is advisable to instal automatic (with all operations) Form–Fill-Seal machines having one continuous operation.

PART IB

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF ORAL SOLID DOSAGE FORMS (TABLETS AND CAPSULES)

Note: - *The General Requirements as given in Part 1 of this Schedule relating to requirements of Good Manufacturing Practices for Premises and materials for pharmaceutical products shall be complied with, mutatis mutandis, for the manufacture of oral Solid Dosage Forms (Tablets and Capsules). In addition to these requirements, the following Specific Requirement shall also be followed, namely :-*

1. *General:*

1.1 The processing of dry materials and products creates problems of dust control and cross-contamination. Special attention is therefore, needed in the design, maintenance and use of premises and equipment in order to overcome these problems. Wherever required, enclosed dust control manufacturing systems shall be employed.

1.2. Suitable environmental conditions for the products handled shall be maintained by installation of air-conditioning wherever necessary. Effective air-extraction systems, with discharge points situated to avoid contamination of other products and processes shall be provided. Filters shall be installed to retain dust and protect the factory and local environment.

1.3. Special care shall be taken to protect against subsequent contamination of the product by particles of metal or wood. The use of metal detector is recommended. Wooden equipment should be avoided. Screens, sieves, punches and dies shall be examined for wear and tear or for breakage before and after each use.

1.4. All ingredients for a dry product shall be sifted before use unless the quality of the input material can be assured. Such sifting shall normally be carried out at dedicated areas.

1.5. [1][Where the facilities are designed to provide special environmental conditions of pressure differentials between rooms, these conditions shall be regularly monitored and any deviation shall be brought to the immediate attention of the production and quality assurance departments].

1.6. Care shall be taken to guard against any material lodging and remaining undetected in any processing or packaging equipment. Particular care shall be taken to ensure that any vacuum, compressed air or air-extraction nozzles are kept clean and that there is no evidence of lubricants leaking into the product from any part of the equipments.

2. ***Sifting, Mixing and Granulation:***

2.1. Unless operated as a closed system, mixing, sifting and blending equipments shall be fitted with dust extractors [1][or in a dedicated area for each operation].

2.2. Residues from sieving operations shall be examined periodically for evidence of the presence of unwanted materials.

2.3. Critical operating parameters like time and temperature for each mixing, blending and drying operation shall be specified in a Master Formula, monitored during processing, and recorded in the batch records.

2.4. Filter bags fitted to fluid-bed dryer shall not be used for different products, without being washed in-between use. With certain highly potent or sensitizing products, bags specific to one product only shall be used. Air entering the dryer shall be filtered. Steps shall be taken to prevent contamination of the site and local environment by dust in the air leaving the dryer due to close positioning of the air-inlets and exhaust.

2.5. Granulation and coating solutions shall be made, stored and used in a manner which minimizes the risk of contamination or microbial growth.

3. ***Compressions (Tablets):***

3.1. Each tablet compressing machine shall be provided with effective dust control facilities to avoid cross-contamination. Unless the same product is being made on each machine, or unless the compression machine itself provides its own enclosed air controlled environment, the machine shall be installed in separate cubicles.

3.2. Suitable physical, procedural and labelling arrangements shall be made to prevent mix up of materials, granules and tablets on compression machinery.

3.3. Accurate and calibrated weighing equipment shall be readily available and used for in-process monitoring of tablet weight variation. Procedures used shall be capable of detecting out-of-limits tablets.

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1. Ins. by G.S.R. 431(E), dt. 30.6.2005.

3.4. At the commencement of each compression run and in case of multiple compression points in a compression machine, sufficient individual tablets shall be examined at fixed intervals to ensure that a tablet from each compression station or from each compression point has been inspected for suitable pharmacopoeial parameters like 'appearance', 'weight variation', 'disintegration', 'hardness', 'friability' and 'thickness'. The results shall be recorded as part of the batch documentation.

3.5. Tablets shall be de-dusted, preferably by automatic device and shall be monitored for the presence of foreign materials besides any other defects.

3.6. Tablets shall be collected into clean, labelled containers.

3.7. Rejected or discarded tablets shall be isolated in identified containers and their quantity recorded in the Batch Manufacturing Record.

3.8 In-process control shall be employed to ensure that the products remain within specification. During compression, samples of tablets shall be taken at regular intervals of not greater than 30 minutes to ensure that they are being produced in compliance with specified in-process specification. The tablets shall also be periodically checked for additional parameters such as 'appearance', 'weight variation', 'disintegration', 'hardness', 'friability' and 'thickness' and contamination by lubricating oil.

4. ***Coating (Tablets):***

4.1. Air supplied to coating pans for drying purposes shall be filtered air and of suitable quality. The area shall be provided with suitable exhaust system and environmental control (temperature, humidity) measures.

4.2 Coating solutions and suspensions shall be made afresh and used in a manner, which shall minimize the risk of microbial growth. Their preparation and use shall be documented and recorded.

5. ***Filling of Hard Gelatin Capsule:***

Empty capsules shells shall be regarded as 'drug component' and treated accordingly. They shall be stored under conditions which shall ensure their safety from the effects of excessive heat and moisture.

6. ***Printing (Tablets and Capsules)***

6.1. Special care shall be taken to avoid product mix-up during any printing of tablets and capsules. Where different products, or different batches of the same product, are printed simultaneously, the operations shall adequately be segregated. Edible grade colours and suitable printing ink shall be used for such printing.

6.2. After printing, tablets and capsules shall be approved by Quality Control before release for packaging or sale.

7. ***Packaging (Strip and Blister):***

7.1. Care shall be taken when using automatic tablet and capsule counting, strip and blister packaging equipment to ensure that all 'rogue' tablets, capsules or foils from packaging operation are removed before a new packaging operation is commenced. There shall be an independent recorded check of the equipment before a new batch of tablets or capsules is handled.

7.2. Uncoated tablets shall be packed on equipment designed to minimize the risk of cross-contamination. Such packaging shall be carried out in an isolated area when potent tablets or Beta-Iactum containing tablets are being packed.

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1. Ins. by G.S.R. 431(E), dt. 30.6.2005.

7.3. The strips coming out of the machine shall be inspected for defects such as misprint, cuts on the foil, missing tablets and improper sealing.

7.4. Integrity of individual packaging strips and blisters shall be subjected to vacuum test periodically to ensure leak proofness of each pocket strip and blister and records maintained.

PART IC

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF ORAL LIQUIDS (SYRUPS, ELIXIRS, EMULSIONS AND SUSPENSIONS)

Note: *The General Requirements as given in Part I of this Schedule relating to Requirements of Good Manufacturing Practices for Premises and Materials for pharmaceutical products shall be complied with, mutatis mutandis, for the manufacture of (Syrups, Elixirs, Emulsions and Suspensions). In addition to these requirements, the following Specific Requirements shall also be followed, namely:-*

1. ***Building and Equipment***:.

1.1. The premises and equipment shall be designed, constructed and maintained to suit the manufacturing of Oral Liquids. The layout and design of the manufacturing area shall strive to minimize the risk of cross-contamination and mix-ups.

1.2. Manufacturing area shall have entry through double door airlock facility. It shall be made fly proof by use of 'fly catcher' and/or 'air curtain'.

1.3. Drainage shall be of adequate size and have adequate traps, without open channels and the design shall be such as to prevent back flow. Drains shall be shallow to facilitate cleaning and disinfecting.

1.4. The production area shall be cleaned and sanitized at the end of every production process.

1.5. Tanks, containers, pipe work and pumps shall be designed and installed so that they can be easily cleaned and sanitized. Equipment design shall be such as to prevent accumulation of residual microbial growth or cross-contamination.

1.6. Stainless steel or any other appropriate material shall be used for parts of equipments coming in direct contact with the products. The use of glass apparatus shall be minimum.

1.7. Arrangements for cleaning of containers, closures and droppers shall be made with the help of suitable machines/devices equipped with the high pressure air, water and steam jets.

1.8. The furniture used shall be smooth, washable and made of stainless steel [1][or any other appropriate material which is scratch proof, washable and smooth].

2. ***Purified Water***.

2.1. The chemical and microbiological quality of purified water used shall be specified and monitored routinely. The microbiological evaluation shall include testing for absence of pathogens and shall not exceed 100 cfu/ml (as per Appendix 12.5 of IP 1996.)

1. Added by G.S.R. 431(E), dt. 30.6.2005.

2.2. There shall be a written procedure for operation and maintenance of the purified water system. Care shall be taken to avoid the risk of microbial proliferation with appropriate methods like re-circulation, use of UV treatment, treatment with heat and sanitizing agent. After any chemical sanitisation of the water system, a flushing shall be done to ensure that the sanitizing agent has been effectively removed.

3. ***Manufacturing:***

3.1. [1][Manufacturing personnel shall wear wherever required, non-fiber shedding clothing to prevent contamination of the products].

3.2. Materials likely to shed fibre like gunny bags, or wooden pallets shall not be carried into the area where products or cleaned-containers are exposed.

3.3. Care shall be taken to maintain the homogenecity of emulsion by use of appropriate emulsifier and suspensions by use of appropriate stirrer during filling. Mixing and filling processes shall be specified and monitored. Special care shall be taken at the beginning of the filling process, after stoppage due to any interruption and at the end of the process to ensure that the product is uniformly homogenous during the filling process.

3.4. The primary packaging area shall have an air supply which is filtered through 5 micron filters. The temperature of the area shall not exceed 30 degrees centigrade.

3.5. When the bulk product is not immediately packed, the maximum period of storage and storage conditions shall be specified in the Master Formula. The maximum period of storage time of a product in the bulk stage shall be validt..

PART ID

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF TOPICAL PRODUCTS , *i.e.* EXTERNAL PREPARATIONS (CREAMS, OINTMENTS, PASTES, EMULSIONS, LOTIONS, SOLUTIONS, DUSTING POWDERS AND IDENTICAL PRODUCTS)

Note*:* *The General Requirements as given in Part I of this Schedule relating to Requirements of Good Manufacturing Practices for Premises and Materials for pharmaceutical products shall be complied with, mutatis mutandis, for the manufacture of Topical Products i.e. External preparations (Creams, Ointments, Pastes, Emulsions, Lotions, Solutions, Dusting powders and identical products used for external applications). In addition to these requirements, the following Specific Requirements shall also be followed, namely: -*

1. The entrance to the area where topical products are manufactured shall be through a suitable airlock. Outside the airlock, insectocutors shall be installed.

2. The air to this manufacturing area shall be filtered through at least 20µ air filters and shall be air-conditioned. [2] [***].

3. The area shall be fitted with an exhaust system of suitable capacity to effectively remove vapours, fumes, smoke, floating dust particles.

4. The equipment used shall be designed and maintained to prevent the product from being accidentally contaminated with any foreign matter or lubricant.

5. [3][Suitable cleaning equipment and material] shall be used in the process of cleaning or drying the process equipment or accessories used.

1. Subs. by G.S.R. 431(E), dt. 30.6.2005.
2. The words "The air shall be ventilated." omitted by G.S.R. 431(E), dt. 30.6.2005.
3. Subs. by G.S.R. 431(E), dt. 30.6.2005, for " no rags or dusters".

6. Water used in compounding shall be Purified Water IP.

7. Powders, wherever used, shall be suitably sieved before use.

8. Heating vehicles and a base like petroleum jelly shall be done in separate mixing area in suitable stainless steel vessels, using steam, gas, electricity, solar energy, etc.

9. A separate packing section may be provided for primary packaging of the products.

PART 1E

SPECIFIC REQUIREMENTS FOR MANUFACTURE OF METERED-DOSE-INHALERS (MDI)

Note*: The General Requirements as given in Part I of this Schedule relating to Requirements of Good Manufacturing Practices for Premises and Materials for pharmaceutical products shall be complied with, mutatis mutandis, for the manufacture of Metered-Dose-Inhalers (MDI). In addition to these requirements, the following Specific Requirements shall also be followed, namely: -*

1. *General:*

Manufacture of Metered-Dose-Inhalers shall be done under conditions which shall ensure minimum microbial and particulate contamination. Assurance of the quality of components and the bulk product is very important. Where medicaments are in suspended state, uniformity of suspension shall be established.

2. *Building and Civil Works:*

2.1. The building shall be located on a solid foundation to reduce risk of cracking walls and floor due to the movement of equipment and machinery.

2.2 All building surfaces shall be impervious, smooth and non-shedding. Flooring shall be continuous and provided with a cove between the floor and the wall as well as the wall to the ceiling. Ceiling shall be solid, continuous and covered to walls. Light fittings and air-grills shall be flush with the ceiling. All service lines requiring maintenance shall be erected in such a manner that these are accessible from outside the production area.

2.3. The manufacturing area shall be segregated into change rooms for personnel, container preparation area, bulk preparation and filling area, quarantine area and spray testing and packing areas.

2.4. Secondary change rooms shall be provided for operators to change from factory clothing to special departmental clothing before entering the manufacturing and filling area.

2.5. Separate area shall be provided for de-cartoning of components before they are air washed.

2.6. The propellants used for manufacture shall be delivered to the manufacturing area distribution system by filtering them through 2μ filters. The bulk containers of propellants shall be stored, suitably identified, away from the manufacturing facilities.

3. *Environmental Conditions:*

3.1. Where products or clean components are exposed, the area shall be supplied with filtered air of Grade C.

3.2. The requirements of temperature and humidity in the manufacturing area shall be decided depending on the type of product and propellants handled in the facility. Other support areas shall have comfort levels of temperature and humidity.

3.3. There shall be a difference in room pressure between the manufacturing area and the support areas and the differential pressure shall be not less than 15 Pascals (0.06 inches or 1.5 mm water gauge).

3.4. There shall be a written schedule for the monitoring of environmental conditions. Temperature and humidity shall be monitored daily.

4. *Garments:*

4.1. Personnel in the manufacturing and filling section shall wear suitable single-piece-garment made out of non-shedding, tight weave material. Personnel in support areas shall wear clean factory uniforms.

4.2. Gloves made of suitable material having no interaction with the propellants shall be used by the operators in the manufacturing and filling areas. Preferably, disposable gloves shall be used.

4.3. Suitable department-specific personnel protective equipment like footwear and safety glasses shall be used wherever hazard exists.

5. *Sanitation:*

5.1. There shall be written procedures for the sanitation of the MDI manufacturing facility. Special care should be taken to handle residues and rinses of propellants.

5.2. Use of water for cleaning shall be restricted and controlled. Routinely used disinfectants are suitable for sanitizing the different areas. Records of sanitation shall be maintained.

6. *Equipment:*

6.1. Manufacturing equipment shall be of closed system. The vessels and supply lines shall be of stainless steel.

6.2. Suitable check weights, spray testing machines and labelling machines shall be provided in the department.

6.3. All the equipment shall be suitably calibrated and their performance validt. on receipt and thereafter periodically.

7. *Manufacture:*

7.1. There shall be an approved Master Formula Records for the manufacture of metered dose inhalers. All propellants, liquids and gases shall be filtered through 2µ filters to remove particles.

7.2. The primary packing material shall be appropriately cleaned by compressed air suitably filtered through 0.2μ filter. The humidity of compressed air shall be controlled as applicable.

7.3. The valves shall be carefully handled and after de-cartoning, these shall be kept in clean, closed containers in the filling room.

7.4. For suspensions, the bulk shall be kept stirred continuously.

7.5. In-process controls shall include periodical checking of weight of bulk formulation filled in the containers. In a two-shot-filling process (liquid filling followed by gaseous filling), it shall be ensured that 100% check on weight is carried out.

7.6. Filled containers shall be quarantined for a suitable period established by the manufacturer to detect leaking containers prior to testing, labelling and packing.

8. ***Documentation-***

8.1. In addition to the routine good manufacturing practices documentation, manufacturing records shall show the following additional information:-

(1) Temperature and humidity in the manufacturing area.

(2) Periodic filled weights of the formulation.

(3) Records of rejections during on-line check weighing.

(4) Records of rejection during spray testing.

PART 1F

SPECIFIC REQUIREMENTS OF PREMISES, PLANT AND MATERIALS FOR MANUFACTURE OF ACTIVE PHARMACEUTIAL INGREDIENTS (BULK DRUGS)

Note: *The General Requirements as given in Part I of this Schedule relating to Requirements of Good Manufacturing Practices for premises and Materials for pharmaceutical products shall be complied with, mutatis mutandis, for the manufacture of active pharmaceutical ingredients (Bulk Drugs). In addition to these requirements, the following Specific Requirements shall also be followed, namely: -*

1. ***Building and Civil Works:***

1.1. Apart from the building requirements contained in Part I, General ante, the active pharmaceutical ingredients facilities for manufacture of hazardous reactions, Beta-Lactum antibiotics. Steroids and Steroidal Hormones / Cytotoxic substances shall be provided in confined areas to prevent contamination of the other drugs manufactured.

1.2. The final stage of preparation of a drug, like isolation/filtration/drying/ milling / sieving and packing operations shall be provided with air filtration systems including pre-filters and finally with a 5 micron filter. Air handling systems with adequate number of air changes per hour or any other suitable system to control the air borne contamination shall be

provided. Humidity / Temperature shall also be controlled for all the operations wherever required.

1.3. Air filtration systems including pre-filters and particulate matter retention air filters shall be used, where appropriate, for air supplies to production areas. If air is re-circulated to production areas, measures shall be taken to control re-circulation of floating dust particles from production. In areas where air contamination occurs during production, there shall be adequate exhaust system to control contaminants.

1.4. Ancillary area shall be provided for Boiler-house. Utility areas like heat exchangers, chilling workshop, store and supply of gases shall also be provided.

1.5. For specified preparation like manufacture of sterile products and for certain antibiotics, sex hormones, cytotoxic and oncology products, separate enclosed areas shall be designed. The requirements for the sterile active pharmaceutical ingredient shall be in line with the facilities required for formulation to be filled aseptically.

2. *Sterile Products:*

Sterile active pharmaceutical ingredient filled aseptically shall be treated as formulation from the stage wherever the process demands like crystallization, lyophilisation, filtration etc. All conditions applicable to formulations that are required to be filled aseptically shall apply *mutatis mutandis* for the manufacture of sterile active pharmaceutical ingredients involving stages like filtration, crystallization and lyophilisation.

3. *Utilities / Services:*

Equipment like chilling plant, boiler, heat exchangers, vacuum and gas storage vessels shall be serviced, cleaned, sanitized and maintained at appropriate intervals to prevent mal-functions or contamination that may interfere with safety, identity, strength, quality or purity of the drug product.

4. *Equipment Design, Size and Location:*

4.1. Equipment used in the manufacture, processing, packing or holding of an active pharmaceutical ingredient shall be of appropriate design, adequate size and suitably located to facilitate operations for its intended use and for its cleaning and maintenance.

4.2. If equipment is used for different intermediates and active pharmaceutical ingredients, proper cleaning before switching from one product to another becomes particularly important. If cleaning of a specific type of equipment is difficult, the equipment may need to be dedicated to a particular intermediate or active pharmaceutical ingredient.

4.3. The choice of cleaning methods, detergents and levels of cleaning shall be defined and justified. Selection of cleaning agents (e.g. solvents) should depend on :

(a) the suitability of the cleaning agent to remove residues of raw materials; intermediates, precursors, degradation products and isomers, as appropriate.
(b) whether the cleaning agent leaves a residue itself;
(c) compatibility with equipment construction materials like centrifuge/ filtration, dryer/fluid bed dryer, rotocone proton dryer, vacuum dryer, frit mill, multi-mill/jet mills/sewetters cut sizing;
(d) test for absence of intermediate or active pharmaceutical ingredient in the final rinse.

4.4. Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils used in the manufacture, processing, packing or holding of active pharmaceutical ingredients. These procedures shall include but should not be limited to the following :

(a) assignment of responsibility for cleaning and maintaining equipment;
(b) maintenance and cleaning program schedules, including where appropriate, sanitizing schedules;
(c) a complete description of the methods and materials used to clean and maintain equipment, including instructions for de-assembling and re-assembling each article of equipment to ensure proper cleaning and maintenance.;
(d) removal or obliteration of previous batch identification;
(e) protection of clean equipment from contamination prior to use;
(f) inspection of equipment for cleanliness immediately before use;
(g) establishing the maximum time that may elapse between completion of processing and equipment cleaning as well as between cleaning and equipment reuse.

4.5. Equipment shall be cleaned between successive batches to prevent contamination and carry-over of degraded material or contaminants unless otherwise established by validation.

4.6. As processing approaches the final purified active pharmaceutical ingredient, it is important to ensure that incidental carry over between batches does not have adverse impact on the established impurity profile. However, this does not generally hold good for any biological, active pharmaceutical ingredient where many of the processing steps are accomplished aseptically and where it is necessary to clean and sterilize equipment between batches.

5. ***In-Process Controls:***

5.1. In-process control for chemical reactions may include the following:

(a) reaction time or reaction completion;
(b) reaction mass appearance, clarity, completeness or pH solutions;
(c) reaction temperature;
(d) concentration of a reactant;
(e) assay or purity of the product;
(f) process completion check by TLC / any other means.

5.2. In-process control for physical operations may include the following:

(a) appearance and colour;
(b) uniformity of the blend;
(c) temperature of a process;
(d) concentration of a solution;
(e) processing rate or time;
(f) particle size analysis;
(g) bulk/tap density;
(h) pH determination;
(i) moisture content.

6. *Product Containers and Closures:*

6.1. All containers and closures shall comply with the pharmacopoeial or any other requirement, suitable sampling methods, sample sizes, specifications, test methods, cleaning procedures and sterilization procedures, when indicated, shall be used to assure that containers, closures and other component parts of drug packages are suitable and are not reactive, additive, adsorptive or leachable to an extent that significantly affects the quality or purity of the drug.

6.2. The drug product container shall be tested or re-examined as appropriate and approved or rejected and shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which these are unsuitable.

6.3 Container closure system shall provide adequate protection against foreseeable external factors in storage / transportation and use that may cause deterioration or contamination of the active pharmaceutical ingredient.

6.4. Bulk containers and closures shall be cleaned and, where indicated by the nature of the active pharmaceutical ingredient, sterilized to ensure that they are suitable for their intended use.

6.5. The container shall be conspicuously marked with the name of the product and the following additional information concerning :

(a) quality and standards, if specified;
(b) manufacturing licence number/drug master file number (whichever applicable), batch number;
(c) date of manufacture and date of expiry;
(d) method for container disposal (label shall give the methodology, if required);
(e) storage conditions, if specified and name and address of the manufacturer, if available.

6.6. Areas for different operation of active pharmaceutical ingredients (bulk drugs) section shall have appropriate area which may be suitably partitioned for different operations.

PART II

REQUIREMENTS OF PLANT AND EQUIPMENT

1. *External Preparations:*

The following equipment is recommended for the manufacture of 'External preparations' i.e. Ointments, Emulsion, Lotions, Solutions, Pastes, Creams, Dusting powders and such identical products used for external applications, whichever is applicable, namely :-

(1) [1][Mixing and storage tanks preferably of stainless steel or any other appropriate material].
(2) [2][Stainless steel container] (steam, gas or electrically heated).
(3) Mixer (electrically operated).
(4) Planetary mixer.
(5) A colloid mill or a suitable emulsifier.
(6) A triple roller mill or an ointment mill.

1. Subs. by G.S.R. 431(E), dt. 30.6.2005; for "mixing and storage tanks (Stainless steel)".
2. Subs. by G.S.R. 431(E), dt. 30.6.2005; for "Jacketted Kettle".

(7) Liquid filling equipment (electrically operated).
(8) Jar or tube filling equipment [1] [***]

Area. - (1) A minmum area of thirty square meters for basic installation and ten square meters for Ancillary area is recommended.

(2) Areas for formulations meant for external use and internal use shall be separately provided to avoid mix-up.

[2][**Note:** The requirement for ancillary area in this part shall not apply to units registered before 1st January, 2002.]

2. ***Oral Liquid Preparations:***

The following equipments are recommended for the manufacture of oral/internal use preparations i.e. Syrups, Elixirs, Emulsions and Suspensions, whichever is applicable, namely: -

(1) [3][Mixing and storage tanks preferably of Stainless steel or any other appropriate material].
(2) Jacketted Kettle / Stainless steel tank (steam, gas or electrically heated).
(3) Portable stirrer (electrically operated).
(4) A colloid mill or suitable emulsifier (electrically operated).
(5) Suitable filtration equipment (electrically operated).
(6) Semi-automatic/automatic bottle filling machine.
(7) Pilfer proof cap sealing machine.
(8) Water distillation unit or deionizer.
(9) Clarity testing inspection units.

Area. - A minimum area of thirty square meters for basic installation and ten square meters for Ancillary area is recommended.

[2][**Note:** The requirement for ancillary area in this part shall not apply to units registered before 1st January, 2002.]

3. ***Tablets:***

The Tableting section shall be free from dust and floating particles and may be air-conditioned. For this purpose, each [4][tablet compression machine] shall be isolated into cubicles and connected to a vacuum dust collector or an exhaust system. For effective operations, the tablet production department shall be divided into four distinct and separate sections as follows: -

(a) Mixing, Granulation and Drying section.
(b) Tablet compression section.
(c) Packaging section (strip/blister machine wherever required).
(d) Coating section (wherever required).

3.1. The following electrically operated equipments are recommended for the manufacture of compressed tablets and hypodermic tablets, in each of the above sections, namely: -

(a) Granulation-cum-Drying section:

(1) Disintegrator and sifter.
(2) Powder mixer.
(3) Mass mixer/Planetary mixer/Rapid mixer granulator.

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1. The word 'electrically operated' Omitted by G.S.R. 431(E), dt. 30.6.2005.
2. Ins by G.S.R. 431(E), dt. 30.6.2005.
3 Subs. by G.S.R. 431(E), dt. 30.6.2005, for "mixing and storage tanks (Stainless steel)".
4. Subs. by G.S.R. 431(E), dt. 30.6.2005, for 'tablet machine'.

(4) [1][Granulator wherever required].
(5) Thermostatically controlled hot air oven with trays (preferably mounted on a trolley)/Fluid bed dryer.
(6) Weighing machines.

(b) Compression section:

(1) Tablet compression machine, single/multi punch/rotatory.
(2) Punch and dies storage cabinets.
(3) Tablet de-duster
(4) Tablet inspection unit/belt.
(5) [1][Dissolution test apparatus wherever required].
(6) In-process testing equipment like single pan electronic balance, hardness tester, friability and disintegration test apparatus.
(7) Air-conditioning and dehumidification arrangement (wherever necessary)

(c) Packaging section:

(1) Strip/blister packaging machine.
(2) Leak test apparatus (vacuum system).
(3) Tablet counters (wherever applicable).
(4) Air-conditioning and dehumidification arrangement (wherever applicable).

Area. – A minimum area of sixty square meters for basic installation and twenty square meters for Ancillary area is recommended for un-coated tablets.

(d) Coating section:

(1) Jacketted kettle [2][stainless steel container or any other appropriate material] (steam, gas or electrically heated for preparing coating suspension).
(2) Coating pan (Stainless steel).
(3) Polishing pan (where applicable).
(4) Exhaust system (including vacuum dust collector).
(5) Air-conditioning and Dehumidification Arrangement.
(6) Weighing balance.

[2][**Note:** The requirement for ancillary area in this part shall not apply to units registered before 1st January, 2002.]

3.2. The coating section shall be made dust free with suitable exhaust system to remove excess powder and fumes resulting from solvent evaporation. It shall be air-conditioned and dehumidified wherever considered necessary.

Area. – A minimum additional area of thirty square meters for coating section for basic installation and ten square meters for Ancillary area is recommended.

Separate area and equipment for mixing, granulation, drying, tablet compression, coating and packing shall be provided for Penicillin group of drugs on the lines indicated above. In case of operations involving dust and floating particles, care shall be exercised to avoid cross-contamination.

[2][**Note:** The requirement for ancillary area in this part shall not apply to units registered before 1st January, 2002.]

3.3. 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 granulation, tableting and packing shall be done in this room.

1. Subs. by G.S.R. 431(E), dt. 30.6.2005.
2. Ins. by G.S.R. 431(E), dt. 30.6.2005.

3.4. The manufacture of effervescent and soluble [1] [***] tablets shall be carried out in air-conditioned and dehumidified areas.

4. *Powders:*

The following equipment is recommended for the manufacture of powders, namely:-

(1) Disintegrator.
(2) Mixer (electrically operated).
(3) Sifter.
(4) Stainless steel vessels and scoops of suitable sizes.
(5) Filling equipment [1][***].
(6) Weighing balance.

In the case of operation involving floating particles of fine powder, suitable exhaust system shall be provided. Workers should be provided with suitable masks during operation.

Area. – A minimum area of thirty square meters is recommended to allow for the basic installations. Where the actual blending is to be done on the premises, an additional room shall be provided for the purpose.

[2][**Note:** The requirement for additional room in this part shall not apply to units registered before 1st January, 2002.]

5. *Capsules:*

For the manufacture of capsules, separate enclosed area suitably air-conditioned and dehumidified with an airlock arrangement shall be provided. The following equipment is recommended for filling Hard Gelatin Capsules, namely: -

(1) Mixing and blending equipment (electrically or power driven).
(2) Capsules filling units [1][***].
(3) Capsules counters (wherever applicable).
(4) Weighing balance.
(5) Disintegration test apparatus.
(6) Capsule polishing equipment.

Separate equipment and, filling and packaging areas shall be provided in penicillin and non-penicillin sections. In case of operations involving floating particles of fine powder, a suitable exhaust system shall be provided. Manufacture and filling shall be carried out in air-conditioned area. The room shall be dehumidified.

Area. –A minimum area of twenty-five square meters for basic installation and ten square meters for Ancillary area each for penicillin and non-penicillin sections is recommended.

[2][**Note:** The requirement for ancillary area in this part shall not apply to units registered before 1st January, 2002.]

6. *Surgical Dressing:*

The following equipment is recommended for the manufacture of Surgical Dressings other than Absorbent Cotton Wool, namely:-

(1) Rolling machine.

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1. Omitted by G.S.R. 431(E), dt. 30.6.2005.
2. Ins. by G.S.R. 431(E), dt. 30.6.2005.

(2) Trimming machine.
(3) Cutting equipment.
(4) Folding and pressing machine for gauze.
(5) Mixing tanks for processing medicated dressing.
(6) Hot air dry oven.
(7) Steam sterilizer or dry heat sterilizer or other suitable equipment.
(8) Work tables/benches for different operations.

Area. – A minimum area of thirty square meters is recommended to allow for the basic installations. In case medicated dressings are to be manufactured, another room with a minimum area of thirty square meters shall be provided.

7. ***Ophthalmic Preparations***:.

For the manufacture of Ophthalmic preparations, separate enclosed areas with airlock arrangement shall be provided. The following equipment is recommended for the manufacture under aseptic conditions of Eye-Ointment, Eye-Lotions and other preparations for external use, namely:-

(1) Thermostatically controlled hot air ovens (preferably double ended).
(2) Jacketted kettle/stainless steel tanks (steam, gas or electrically heated).
(3) Mixing and storage tanks of stainless steel/Planetary mixer.
(4) Colloid mill or ointment mill.
(5) Tube filling and crimping equipment (semi-automatic or automatic filling machines).
(6) Tube cleaning equipment (air jet type).
(7) Tube washing and drying equipment, if required.
(8) Automatic vial washing machine.
(9) Vial drying oven.
(10) Rubber bung washing machine.
(11) Sintered glass funnel, Seitz filter and filter candle (preferably cartridge and membrane filters).
(12) Liquid filling equipment (semi-automatic or automatic filling machines).
(13) Autoclave (preferably ventilator autoclave).
(14) Air conditioning and dehumidification arrangement (preferably centrally air-conditioned and dehumidification system).
(15) Laminar airflow units.

Area. – (1) A minimum area of twenty-five square meters for basic installation and ten square meters for Ancillary area is recommended. Manufacture and filling shall be carried out in air-conditioned areas under aseptic conditions. The rooms shall be further dehumidified as considered necessary if preparations containing antibiotics are manufactured.

(2) Areas for formulations meant for external use and internal use shall be separately provided to avoid mix up.

[1][**Note:** The requirement for ancillary area in this Part shall not apply to units registered before 1st January, 2002.]

8. ***Pessaries and Suppositories:***

(i) The following equipment is recommended for manufacture of Pessaries and Suppositories, namely: -

(1) Mixing and pouring equipment
(2) Moulding equipment.
(3) Weighing devices.

1. Ins. by G.S.R. 431(E), dt. 30.6.2005.

Area. – A minimum area of twenty square meters is recommended to allow for the basic installation.

(ii) In the case of pessaries manufactured by granulation and compression, the requirements as indicated under "Item 3 of Tablet", shall be provided.

9. *Inhalers and Vitrallae:*

The following equipment is recommended for manufacture of inhalers and vitrallae, namely: -

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

Area. – An area of minimum twenty square meters is recommended for the basic installations.

10. *Repacking of drugs and pharmaceutical chemicals:*

The following equipment is recommended for repacking of drugs and pharmaceuticals chemicals, namely:-

(1) Powder disintegrator.
(2) Powder sifter (electrically operated).
(3) Stainless steel scoops and vessels of suitable sizes.
(4) Weighing and measuring equipment.
(5) Filling equipment (semi-automatic / automatic machines).
(6) Electric sealing machine.

Area. – An area of minimum thirty square metres is recommended for the basic installation. In case of operations involving floating particles of fine powder, a suitable exhaust system shall be provided.

11. *Parenteral Preparations*

The whole operation of manufacture of parenteral preparations (small volume injectables and large volume parenterals) in glass and plastic containers may be divided into the following separate areas/rooms, namely: -

11.1 *Parenteral preparations in glass* containers*:* –

(1) *Water management area*: This includes water treatment and storage.
(2) *Containers and closures preparation area*: This includes washing and drying of ampoules, vials, bottles and closures.
(3) *Solution preparation area*: This includes preparation and filtration of solution.
(4) *Filling, capping and sealing area*: This includes filling and sealing of ampoules and/or filling, capping and sealing of vials and bottles.
(5) Sterilization area
(6) Quarantine area
(7) Visual inspection area.
(8) Packaging area

The following equipment is recommended for different above-mentioned areas, namely: -

(a) Water management area:

(1) De-ionised water treatment unit.
(2) Distillation (multi-column with heat exchangers) unit.
(3) Thermostatically controlled water storage tank.
(4) Transfer pumps.
(5) Stainless steel service lines for carrying water into user areas.

(b) Containers and closures preparation area:

(1) Automatic rotary ampoule/vial/bottle washing machine having separate air, water distilled water jets.
(2) Automatic closures washing machine,
(3) Storage equipment for ampoules, vials, bottles and closures.
(4) Dryer/sterilizer (double ended)
(5) Dust proof storage cabinets.
(6) Stainless steel benches/stools.

(c) Solution preparation area:

(1) Solution preparation and mixing stainless steel tanks and other containers.
(2) Portable stirrer.
(3) Filtration equipment with cartridge and membrane filters/bacteriological filters.
(4) Transfer pumps.
(5) Stainless steel benches/stools

(d) Filling, capping and sealing area:

(1) Automatic ampoule/vial/bottle filling, sealing and capping machine under laminar air flow workstation.
(2) Gas lines (Nitrogen, Oxygen, Carbon dioxide) wherever required.
(3) Stainless steel benches / stools.

(e) Sterilization area:

(1) Steam sterilizer (preferably with computer control for sterilization cycle along with trolley sets for loading/unloading containers before and after sterilization).
(2) Hot air sterilizer (preferably double ended).
(3) Pressure leak test apparatus.

(f) Quarantine area. –

(1) Storage cabinets.
(2) Raised platforms/steel racks.

(g) Visual inspection area:

(1) Visual inspection units (preferably conveyor belt type and composite white and black assembly supported with illumination).
(2) Stainless steel benches/stools.

(h) Packaging area. -

(1) Batch coding machine (preferably automatic).

(2) Labelling unit (preferably conveyor belt type).
(3) Benches/stools.

Area. – (1) A minimum area of one hundred and fifty square meters for the basic installation and an Ancillary area of one hundred square meters for Small Volume Injectables is recommended. For Large Volume Parenterals, an area of one hundred and fifty square meters each for the basic installation and for Ancillary area is recommended. These areas shall be partitioned into suitable enclosures with airlock arrangements.

(2) Areas for formulations meant for external use and internal use shall be separately provided to avoid mix up.

(3) Packaging materials for large volume parenteral shall have a minimum area of 100 square meters.

[1][**Note:** The requirement for ancillary area in this part shall not apply to units registered before 1st January, 2002.]

11.2 *Parenteral preparations in plastic containers by Form-Fill-Seal/Blow, Fill-Seal Technology.*-The whole operation of manufacture of large volume parenteral preparations in plastic containers including plastic pouches by automatic (all operations in one station) Form-Fill-Seal machine or by semi-automatic blow moulding, filling-cum-sealing machine may be divided into following separate areas/rooms, namely: -

(1) Water management area.
(2) Solution preparation area.
(3) Containers moulding-cum-filling and sealing area.
(4) Sterilization area.
(5) Quarantine area .
(6) Visual inspection area.
(7) Packaging area.

The following equipment is recommended for different above mentioned areas namely: -

(a) Water management area:

(1) De-ionised water treatment unit.
(2) Distillation unit (multi column with heat exchangers).
(3) Thermostatically controlled water storage tank.
(4) Transfer pumps.
(5) Stainless steel service lines for carrying water into user areas.

(b) Solution preparation area:

(1) Solution preparation and storage tanks.
(2) Transfer pumps.
(3) Cartridge and membrane filters.

(c) Container moulding-cum-filling and sealing area:

(1) Sterile Form-Fill-Seal machine (all operations in one station with built-in laminar air flow workstation having integrated container output conveyor belt through pass box).
(2) Arrangement for feeding plastic granules through feeding-cum-filling tank into the machine.

1. Ins. by 431(E), dt. 30.6.2005.

(d) Sterilization area: Super heated steam sterilizer (with computer control for sterilization cycle along with trolley sets for loading/unloading containers for sterilization).

(e) Quarantine area:- Adequate number of platforms/racks with storage system.

(f) Visual inspection area. - Visual inspection unit (with conveyor belt and composite white and black assembly supported with illumination).

(g) Packaging area:

(1) Pressure leak test apparatus (pressure belt or rotating disc type).
(2) Batch coding machine (preferably automatic).
(3) Labelling unit (preferably conveyor belt type).

Area. – (1) A minimum area of two hundred and fifty square meters for the basic installation and an Ancillary area of one hundred and fifty square metres for large volume parenteral preparations in plastic containers by Form-Fill-Seal technology is recommended. These areas shall be partitioned into suitable enclosures with airlock arrangements.

(2) Areas for formulations meant for external use and internal use shall be separately provided to avoid mix up.

(3) Packaging materials for large volume parenteral shall have a minimum area of 100 square meters.]

[1][**Note:** The requirement for ancillary area in this part shall not apply to units registered before 1st January, 2002.]

[1][**Note I:** There are certain categories of drugs such as chemicals and pharmaceutical aids, gauzes and bandages, medicinal gases, empty gelatin capsules, non- chemical/mechanical contraceptives, diagnostic kits and reagents, medical devices, new dosage forms and their delivery systems, disinfectant fluids, antacids, raw-materials manufactured from sea bittern, veterinary biologicals including poultry vaccines, re-packing of drugs, etc. for which this Schedule does not prescribe specific requirements of space and equipments. The Licensing Authority, as the case may be, in respect of such categories of drugs, have the discretion to modify the requirements of this Schedule, if he is of the opinion that having regard to the nature off the products and extent of manufacturing operations and for reasons to be recorded in writing, it is necessary to relax or alter them in the circumstances of a particular case and direct the manufacturer to carry out necessary modifications in them and the modifications having been made, approve the manufacturer of such categories of the drugs.

Note II: In case of manufacturers licensed to manufacture drugs prior to the 11th December, 2001, the requirements of this Schedule shall also apply to them from 1st July, 2005.]

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1. Ins. by G.S.R. 431(E), dt. 30.6.2005.

[1] [SCHEDUE M-I

[*See* Rule 85E (2)]

GOOD MANUFACTURING PRACTICES AND REQUIREMENTS OF PREMISES, PLANT AND EQUIPMENT FOR HOMOEOPATHIC MEDICINES

1.GENERAL REQUIREMENTS:

1.1 Location and Surroundings: - The premises shall be situated at a clean place which shall not be adjacent to open drains, public lavatory or any factory producing pollution of any kind, garbage dump, slaughter house or any other source likely to cause contamination from the external environment. The premises shall be located away from railway lines so that the performance of sensitive electronic equipment is not affected by vibrations. There shall be no open drains inside or outside the manufacturing premises. It shall be so designed that the entry of rodents is checked. The drains shall facilitate easy flow of the effluent and shall be cleared periodically.

1.2 Building: - The premises shall not be used for any purpose other than manufacture of homoeopathic drugs and no part of the manufacturing premises shall be used for any other purpose. Other facilities, if needed, could be provided in separate building(s) in the same campus. Crude raw materials, packing materials, etc. shall be stored and handled in places earmarked for them and shall not be taken inside areas where critical operations of manufacture are done excepting processed raw material. Heating, washing, drying, packing and labelling etc. wherever needed, shall be done in dedicated ancillary areas adjacent to the manufacturing sections concerned. The walls and floorings of manufacturing areas shall be smooth and free from chinks, cracks and crevices and shall be washable. The design of the windows, windowpanes and all fittings shall be such that they will not facilitate accumulation / lodging of dust and other contaminants.

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1. *Subs. by G.S.R. No. 678(E) , dt. 31-10-2006, for Schedule MI. Earlier Schedule MI was inserted by G.S.R. 507 (E), dt: 12.6.1987. Schedule M1, before substitution, stood as under.:*

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SCHEDUE M-I

[*See* Rule 85E (2)]

1. Requirement of factory premises for manufacture of Homeopathic preparations-

(a) *Location and surroundings*. - The factory shall be situated in a place which shall not be adjacent to an open sewage drain, public lavatory or any factory which produces a disagreeable or obnoxious odour or fumes or large quantities of soot, dust or smoke. The factory shall be located in a sanitary place, remove from filthy surroundings.

(b) *Buildings*. - The part of the building used for manufacturing shall not be used for a sleeping place and no sleeping place adjoining to it shall communicate therewith except through open air or through an intervening open space. The walls of the room in which manufacturing operations are carried out shall, upto a height of six feet from the floor, be smooth, waterproof and shall be capable of being kept clean. The flooring shall be smooth, even and washable and shall be such as not to permit retention or accumulation of dust. There shall be no chinks or crevices in the walls or floor.

(c) The building used for the factory shall be constructed so as to permit production under hygienic conditions laid down in the Factories Act, 1948 (63 of 1948).

(d) *Water Supply*. - The water used in manufacture shall be pure and drinkable quality, free from pathogenic microorganisms.

(e) *Disposal of waste*. - There should be adequate arrangement for disposal of waste-water and other residues from the laboratory.

(f) The rooms should be airy and clean and the temperature of the room should be moderately comfortable.

(g) *Health, Clothing and Sanitary requirement of the Staff.* - All workers shall be free from contagious or obnoxious disease. Their clothing shall consist of a white or coloured uniform suitable to the nature of the work and the climate, and shall be clean. Adequate facilities for personal cleanliness, such as clean towels, soap and hand scrubbing brushes, shall be provided separately for each sex. The workers shall be required to wash and change into clean footwear before entering the rooms where the manufacturing operations are carried on. Workers shall be required to wear either a clean cap or a suitable headgear so as to avoid any possibility of contamination by air or perspiration.

(h) *Medical services.* - The manufacturer shall provide adequate facilities for First Aid, Medical inspection of workers at the time of employment and periodically check-up thereafter at least once a year.

(i) *Working benches.* - Working benches shall be provided for carrying out operations such as filling, labelling, packing etc. Such benches shall be fitted with smooth, impervious tops capable of being washed.

(j) *Container management*. - Where operations involving use of containers such as bottles, phials and jars are conducted, there shall be adequate arrangements separated from potentisation chamber for washing, cleaning and drying such containers, with suitable equipment for the purpose. Wherever these are attended manually adequate precaution of perfection in respect of cleanliness and avoidance of pollutants shall be taken.

2. Requirements of Plant and Equipment:

(a) Mother tinctures. External tinctures and Mother solution section. - The following plant and equipment shall be provided namely: -

(i) Disintegrator.
(ii) Sieved Separator.
(iii) Balances and fluid measures.
(iv) Chopping boards and knives.
(v) Macerators with lids.
(vi) Percolators with lids and regulated discharge.
(vii) Moisture determination apparatus or other suitable arrangement.
(viii) Filtering arrangement.
(ix) Mixing vessels and suitable non-metallic storage containers.
(x) Portable stirrers.
(xi) Water still.

Note*:* (1) As far as possible metal contacts may be avoided once the drug is processed. (2) An area of 55 sq. meters is recommended for basic installations.

(3) Adequate separate storage facility should be provided for raw material quarantine, storage and bonded room for alcohol where applicable.

(4) Separate and suitable storage facility should be provided for fresh herbs and odorous raw materials.

(5) Adequate laboratory facility shall be provided for testing of raw materials and finished products,

(b) Potentisation Section. - (1) The following arrangements are recommended for container for closure preparation section namely:

(i) Washing tanks with suitable brushing arrangement manual or mechanical.
(ii) Purified Water rinsing tank
(iii) Closure macerating or washing tanks.
(iv) Drying chambers.

An area of 20 sq. meters is recommended for basic installations.

(2) The following arrangements are recommended for potency preparation section, namely:

(i) Working tables with washable top.
(ii) Facilities for separate storage of different grades of back potencies.
(iii) Suitable measuring devices for discharge of drug and diluent in potentisation vial,
(iv) Potentiser with counter or suitable manual arrangement.

Note: - (1) Different droppers shall be used for different drugs potencies.

(2) All measuring devices shall be of metric system and be made of glass and shall be free from metallic contents.

(3) It is desired that glass droppers etc. intended for re-use after cleaning should be sterilized by autoclave or heating in a hot air oven.

(4) Plastics, rubber tubes, bulks etc. coming in contact with tinctures or back potencies should not be re-used for other tincture and potencies.

(5) Method of potentisation will be adopted as specified in Homoeopathic Pharmacopoeia of India Vol. I.

3. Triturating, Tableting and Pill/Globules section -

(3) The following arrangements are recommended: (i)

Triturating machine for suitable device.
(ii) Disintegrator.
(iii) Mass Mixer. (iv)
Granulator. (v)
Oven.
(vi) Tableting punches or machines.
(vii) Kettle (Steam/gas/electrically heated) for preparation solution. (viii) Dryers.
(ix) Sieved separator, tablet counters and balances.

Note: Tablet section shall be free from dust and floating particles. An area of 55 sq. meters is recommended for basic installations.

(4) Ointments and lotion section:

The following arrangements are recommended namely: -

(i) Mixing tank
(ii) Kettle (Steam, gas or electrically heated). (iii)
Suitable powder mixer
(iv) Ointment mill
(v) Filling equipment or arrangement.

An area of 20 sq. meters is recommended for basic installations. (5) Syrups

and tonics:

The following arrangements are recommended namely:- (i)
Mixing and storage tank.
(ii) Potable mixer.
(iii) Filtering equipment. (iv)
Water still / Deioniser.
(v) Filling and sealing equipment.

An area of 20 sq. meters is recommended for basic installations. (6)

Ophthalmic Preparations:

The following equipment is recommended for manufacture under aseptic conditions of Eye-Ointments, Eye-Drops, Eye-lotions and other preparations for external use, namely: -

(i) Hot air even electrically heated with thermostatic control. (ii) Colloid mill or ointment mill.
(iii) Kettle (gas or electrically heated) with suitable mixing arrangement. (iv) Tube filling equipment.
(v) Mixing and storage tanks of stainless steel or of other suitable material.
(vi) Sintered glass funnel, Seitz filter or filter candle. (vii) Liquid filling equipment.
(viii) Autoclaves.

Adequate precaution should be taken to ensure that the finished product is sterile. An area of 20 sq. meters is recommended for basic installations.

(7) Adequate arrangements for space and equipment should be made for labelling and packing."

2. PLANT AND EQUIPMENT:

2.1 General: - The design of the plant shall be suitable for the nature and quantum of the activities involved. Equipment shall be installed in such a manner as to facilitate easy flow of materials and to check criss-cross movement of the personnel. The entry to all manufacturing sections shall be regulated and persons not associated with the activities in the sections shall not have access to them. There shall be arrangements for personal cleanliness of workers and toilets. These shall be separate for men and women workers. There shall be suitable arrangement, separate for men and women, to change from their outside dress and footwear into the factory dress and footwear. Uniforms of suitable colours and fabric which facilitate proper washing and which do not shed fibres other contaminants shall be provided. Suitable head-covers and gloves shall be provided to the workers. The manufacturing premises shall not be used for dining. There shall be separate area for the personnel to take food or rest. Toilets shall be located in or adjacent to any of the areas concerned with any manufacturing activity. Spitting, smoking, chewing, littering, etc. in the manufacturing or ancillary areas shall not be permitted. Standard operating practices (SOPs) for cleaning and sanitation, personal hygiene of the workers, general and specific upkeep of the plant, equipment and premises and every activity associated with manufacture of drugs including procurement, quarantine, testing and warehousing of material shall be written and adopted. No person with any contagious disease shall be involved in any of the manufacturing activities. There shall be proper arrangements for maintenance of the equipment and systems. The performance of every equipment and system shall be properly validated and their use shall be monitored. Dos and don'ts in the matter of the use of the plant and equipment as may be applicable shall be written and displayed in all places.

There shall be separate dedicated areas for each ancillary activity such as receipt, cleaning, warehousing and issue of raw materials, packaging materials, containers and closures, finished goods etc. Adequate measures shall be taken to prevent entry/presence etc. of insects, rodents, birds, lizards and other animals into the raw material handling areas. Every material shall have proper identification and control numbers and inventory tags and labels displaying status of the quality being used, etc. There shall be proper arrangements and SOPs for preventing mix-up of materials at every stage of handling. There shall be separate arrangements for handling and warehousing of materials of different origins. Materials with odour shall be kept in tightly closed containers and shall be well protected from other materials. Fresh materials and odorous materials shall, preferably be stored in separate dedicated areas. Where bonded manufacturing and / or warehousing facilities are required as per

Excise laws, the facilities required shall be provided without compromise on the requirements specified above.

A well equipped laboratory for quality control/quality assurance of raw materials and finished products and for carrying out in-process controls shall be provided.

(a) Rooms: - The rooms shall be airy, ventilated, and maintained at temperatures which are moderate and comfortable. Sections which are required to be sterile, air-conditioned and provided with air handling system shall be designed accordingly. All sections shall be free from insects, birds, rodents, worms etc. and suitable measures shall be taken to prevent the same from finding ways to the sections and equipment.

(b) Water: - The water used for manufacture of drugs shall be of the quality as prescribed in the rules or in the Homoeopathic Pharmacopoeia concerned, as the case may be, and shall be prepared from pure drinking quality water, free from pathogenic organisms.

(c) Disposal of waste: - Effluents, organic and inorganic wastes shall be disposed of in such a manner as may be prescribed in the laws pertaining to pollution control and if no such law exists in the place of manufacture, they shall be rendered harmless and shall be disposed of in such a manner that they are not hazardous to health of the public or cattle or plants.

(d) Factories Act: - The provisions of the Factories Act, 1948(Act 63 of 1948), as applicable shall be adhered to.

(e) Medical Services:- All persons concerned with any activity pertaining to manufacture of drugs including handling of raw materials, packing materials, packing and labelling of drugs, etc. shall be medically examined for fitness at the time of employment and subsequently at periodic intervals and records thereof shall be maintained.

(f) Safety measures: - First-aid facilities shall be provided in such a manner that they are easily accessible and staff shall be imparted knowledge and training in first-aid measures as may be needed. Fire control equipment in suitable numbers shall be provided at easily accessible places near all sections including stores and warehouses.

(g) Workbenches: - Workbenches suitable to the nature and quantum of the work involved shall be provided in all sections. Such work benches in general, shall have smooth, washable and impervious tops and the parts shall not be rough or rusty or damaged otherwise.

(h) Container management: - Proper arrangements shall be made for receiving containers, closures and packing materials in secluded areas and for de-dusting the same, removal of wastes, washing, cleaning and drying. Suitable equipment shall be provided as may be needed, considering the nature of work involved. Where soaps and detergents are used to wash containers and closures used for primary packing, suitable procedure shall be prescribed and adopted for total removal of such materials from the containers and closures. Plastic containers which are likely to absorb active principle or which are likely to contaminate the contents may not be used.

Glass containers used shall be made of neutral glass. The closures and washers used shall be of inert materials which shall not absorb the active principles or contaminate the contents or which may otherwise be likely to cause deterioration of quality. The containers, closures and packing materials shall protect the properties of the medicines, Tablets, if blister-packed, shall have secondary protective packaging to protect the medicines from moisture, odour etc. Neutral glass phials and epoxy-coated closure shall be used for eye-drops. Transparent plastic containers may be used for eye-drops containing only aqueous preparations. Sterile plastic nozzles may be provided to eye-drops separately along with the medicine, whatever needed.

2.2. Personnel.- Manufacture of drugs shall be under the control of approved technical staff that shall possess the qualifications prescribed in rule 85.

3. REQUIREMENT OF EQUIPMENT AND FACILITIES:

3.1 Mother tinctures and mother solutions:- The following equipment and facilities shall be provided:-

(i) Disintegrator;
(ii) Sieved separator;
(iii) Balances, weights and fluid measures, all in metric system;
(iv) Chopping table/board and knives;
(v) Macerators with lids (all made of stainless steel of grade 304 or neutral glass);
(vi) Percolators (all made of stainless steel of grade 304);
(vii) Moisture determination apparatus;
(viii) Filter press/Sparkler filter (all metal parts shall be of stainless steel);
(ix) Mixing and storage vessels (Stainless steel of grade 304);
(x) Portable stirrers (Rod, blades and screws shall be of stainless steel);
(xi) Water still/water purifier;
(xii) Macerators and percolators for preparing mother solutions of materials of chemical origin. These shall be of material, which will not react with the chemicals, used and which do not bleach; and
(xiii) Filling and sealing machine.

The area and facilities for manufacture of mother tinctures and mother solutions shall be separate and shall be 55 square meters for each for basic installations.

3.2 Potentisation section :- The section shall have the following facilities:-

(i) Work benches with washable impervious tops;
(ii) Facilities for orderly storage of different potencies and back-potencies of various drugs;
(iii) Suitable devices for measuring and dispensing of potencies/back-potencies into the potentisation phials;
(iv) Potentiser with counter.

An area of 20 square meters shall be provided for basic installations.

Note: -

(a) The requirement of potentiser is not mandatory. The process may be done manually also with proper SOPs. Potentiser, if used, shall be properly validated and shall be calibrated every time before commencement of work for proper performance.

(b) The manufactur er sh all use back-poten cies procur ed fr om Licen sed manufacturers and the firm shall maintain proper records of purchase or shall prepare own-back potencies . Every container of potencies and back-potencies shall be kept properly labelled and there shall not be mix-up of different medicines and different potencies.

3.3 Containers and Closures Section: - Separate area for preparation of containers and closures shall be provided adjacent to the potentisation section. This area shall have the following facilities:-

(i) Washing tanks with suitable mechanical or hand operated brushes;
(ii) Rinsing tanks. Purified water shall be used for rinsing;
(iii) Closures washing / macerating tanks;
(iv) Driers;

Note: -

(a) Different droppers shall be used only for each different medicine and different potency.
(b) All measures shall be in metric system. Measures used shall be of neutral glass. Metal droppers and plastic droppers shall not be used.
(c) Glass droppers shall be reused only after proper cleaning and sterilization.

(d) Potentisation shall be done by the method(s) prescribed in the Homoeopathic Pharmacopoeia of India.

3.4 Trituration, Tableting, Pills and Globules making sections:- The following basic equipment and facilities shall be provided:-

(i) Triturating Machine;
(ii) Disintegrator;
(iii) Mass Mixer;
(iv) Granulator;
(v) Electrical Oven;
(vi) Tablets punching Machine;
(vii) Kettle (steam or electrically heated) for preparing solutions;
(viii) Driers for drying granules and tablets;
(ix) Sieved separator (stainless steel);
(x) Tablet counter;
(xi) Balances;
(xii) Coating Pan with spray-gun;
(xiii) Multi-sifter
(xiv) Mill with perforations.

An area of 55 square meters shall be provided for basic installations. The area shall be suitably divided into cubicles to minimize cross contamination, mix-up etc.

Note: - The section shall be free from insects, worms, rodents, dust and other floating particles and moisture.

3.5 Syrups and other oral liquids section:- The following basic equipment and facilities shall be provided:-

(i) Mixing and storage tanks (stainless steel of grade 304);
(ii) Portable stirrer (rod, blades and screws shall be of stainless steel);
(iii) Filter press / Sparkler filter (all metal parts shall be of stainless steel);
(iv) Filling and sealing machine;
(v) pH meter.

An area of 20 square meters shall be provided for basic installations. The section shall be free from dust and other floating particles, cobwebs, flies, ants and other insects, birds, lizards and rodents.

(1) Adequate number of workbenches shall be provided.

(2) Visual inspection table shall be provided. This shall comprise of a colour con trast backgr ound with lamp for providing diffused ligh t, mounted on a suitable table.

3.6 Ointments and lotions section :- The following basic equipments and facilities shall be provided:-

(i) Mixing tanks (Stainless steel)
(ii) Kettle (steam or electrically heated) for preparing solutions
(iii) Suitable powder / planetary Mixer
(iv) Ointment mill / colloidal Mill / Emulsifier
(v) Filling and sealing machine / Crimping machine
(vi) Filtering equipment
(vii) Balance and weights

A minimum area of 20 square meters shall be provided for basic installations. An ancillary area for washing vessels and equipment shall be provided. An ancillary area for heating purposes shall also be provided.

3.7 Ophthalmic preparations section:- The following basic equipment and facilities shall be provided:-

(i) Hot air oven, electrically heated, with thermostatic control;

(ii) Laminar Air Flow bench;
(iii) Air Handling Unit with HEPA filters to provide filtered air and positive pressure to the section and air-locks;
(iv) Ointment mill / colloidal mill;
(v) Mixing and storage tanks (Stainless steel of grade 304);
(vi) Pressure vessels, as may be needed;
(vii) Sintered glass funnels, Seitz Filter / Filter candle;
(viii) Vacuum pump;
(ix) Filling machines for liquids ointments etc.;
(x) Autoclaves with pressure and temperature gauges; and
(xi) Necessary workbenches, visual inspection bench, etc.

Area: Minimum area of 20 square meters shall be provided for basic installations.

Note: -

1. The section shall have a clean room facility of Class 100 specification.
2. The section shall be air-conditioned and humidity controlled.
3. Entry to the sections shall be regulated through air-locks with differential air pressures with the air-lock adjacent to the section having higher pressure and the first one through which entry is made with the least pressure.
4. Materials shall be passed to the sections through suitable hatches.
5. The personnel shall wear sterile clothing including headgear, which shall not shed fibre.
6. Washing of phials shall be done in separate areas with proper equipment. Proper facilities shall be provided in the area for washing vessels.
7. Separate area shall be provided for packing and labelling.

4. QUALITY CONTROL DIVISION:

4.1 Functions: - A separate quality control division shall be provided in the premises. The section shall be under the control of an approved technical officer, independent of the manufacturing division and directly responsible to the management. The section shall be responsible for ensuring the quality of all raw materials, packing materials and finished goods. The section shall also carry out in-process quality checks of the products. The section shall be responsible for the stability of the products and for prescribing their shelf life wherever applicable.

The functions of the division shall include:-

(1) To test the identity, quality and purity of the raw materials and to recommend rejection of the material of poor quality and approve materials of the prescribed quality only.
(2) To test the identity, quality and purity of the finished products and to recommend rejection of the material of poor quality and to approve materials of the prescribed quality only.
(3) To prepare and validate the methods of analysis, validate the equipment, monitor their use, take steps for proper maintenance, etc.
(4) To approve or reject container s, closures and packaging materials in accordance with the prescribed norms.
(5) To exercise / carry out in-process control of products.
(6) To prescribe SOPs on all matters concerning quality of materials and products.
(7) To monitor the storage and handling of raw materials, finished products, containers, closures and packaging materials.
(8) To investigate complaints on quantity of products and take / recommend appropriate measures and to examine returned goods and recommend their proper disposal.

4.2 Personnel: - The quality control staff shall be full-time personnel. Analysis and tests of drugs, raw materials, etc. shall be done by qualified and approved technical staff. The technical staff shall have the minimum qualification of degree in Homoeopathic Pharmacy or Science with Chemistry or Botany as the principal subject and experience of not less than

two years in the test and analysis of medicines including handling of instruments.

4.3 Equipment: - The following equipment shall be provided:-

(i) Microscope of suitable magnification and photographic device;
(ii) Dissecting microscope;
(iii) TLC apparatus;
(iv) UV lamp viewer;
(v) Monopan Digital Electronic Balance;
(vi) Hot air oven;
(vii) Distillation apparatus;
(viii) Water Bath;
(ix) Polarimeter;
(x) Refractometer;
(xi) Melting point apparatus;
(xii) pH meter;
(xiii) Magnetic stirrer;
(xiv) Table Centrifuge;
(xv) Muffle furnace / electric Bunsen;
(xvi) Moisture determination apparatus;
(xvii) U.V. Spectrophotometer;
(xviii) Rotary microtome / Section cutting facilities;
(xix) Tablet Disintegration Machine.

5. RAW MATERIALS:

5.1 Raw materials of Plant Origin:-

(a) The raw materials of plant origin used for manufacture of drugs shall be of the following specifications:-

(i) the materials shall be those recently collected and dried and shall be free from moisture so as to eliminate the risk of deterioration and infestation with pests moulds, etc. The materials shall be collected when the atmospheric temperature is suitable where its active constituents are not changed / damaged / destroyed.

(ii) when fresh materials are to be used, the time lapse from the time of collection to use shall be minimized to the extent possible;

(iii) the materials should be taken from healthy plants and shall be free from parasites, moulds, etc.;

(iv) the materials shall be free of inorganic or organic foreign matter;

(v) when dry materials are procured, they shall be from healthy plants and shall be in unprocessed form, free from all extraneous matters such as fungus, insects, moulds, pathogenic organisms, etc. and should not be more than six months old. Plant materi alsof Agaricaceae, which are perishable shall be used within one week of ollection.

(b) To facilitate proper identification and purity of the material and to exercise proper quality control of the material, the following conditions must be satisfied:-

(i) a small twig of the plant with leaves shall be available if the part used is bark of the plant;

(ii) an entire plant or part or aerial twig with leaves and some uncut roots / rhizomes / bulbs shall be available if the part used is a root /rhizome / bulb;

(iii) if plants with flowers are to be used, a few dry flowers shall also be available with the aerial twig;

(iv) if the material used is a mould or of the plant families Agaricaceae, Polyporaceae/ amanitacaea / Boletaceae / Russulaceae, a whole specimen plant / mould shall be available in properly dried form;

(v) the materials shall be free from insecticides, fungicides, etc;

(vi) the materials shall be in open mesh bags or in suitable material which permits the passage of air inside;

(vii) each consignment of the material shall be accompanied by a statement of the supplier's name; name of the plant with description of the part supplied. The

pharmacopoeial reference, place of collection /harvest, date and time of collection and packaging and weight.

5.2 Raw material of Chemical origin: - They shall be of respective pharmacopoeial standards and statements of their specification shall accompany the materials.
5.3 Raw materials of animal origin: - The materials shall be those collected from healthy animals and shall be of pharmacopoeial specifications. The materials shall be those collected, packed and transported under proper hygienic conditions and well protected from all contamination. The materials shall be accompanied by statements as in para 'a' above. In case of drugs derived from a whole insect, bulk of such drugs along with some uncut whole insect should be provided / maintained for records.
5.4 Sarcodes: - The materials shall be those collected from healthy animals and shall be of pharmacopoeial specification. The materials shall be those collected, packed and transported under proper hygienic conditions and well protected from all contamination. The materials shall be accompanied by statements as in the Para 'a' above. The materials shall be tested to see that they are free from pathogenic organisms such as E. Coli, Salmonella, etc.
5.5 Nosodes: - These shall be of pharmacopoeial specifications. As these are derived from diseased animals or human beings, they shall be autoclaved immediately after collection and preserved and transported under proper hygienic conditions and well protected from all contamination. Before use, these shall be sterilized by autoclaving and shall comply with the test for sterility as specified in the Homoeopathic Pharmacopoeia.

6. PROCEDURES:
6.1 Manufacture of Mother tinctures: -
(a) Every material shall be identified and checked for its purity. They shall be cleaned and processed by cutting, chopping, etc. for use in macerators / percolators. A specimen of the material shall be preserved till approval of the product for release for sale.
(b) The design and procedures adopted shall ensure reproduction of the product of the same quality every time.
(c) Mother tinctures shall be preserved in tight closed neutral containers at temperatures preferably below 250 C, protected from light.
6.2 Manufacture of Attenuations: -
(a) Attenuations shall be prepared in a clean room environment with filtered air and positive pressure inside suitable for the operations.
(b) The methods used shall be reproducible and shall be validated.
(c) The containers, tubings, etc. of the machines used for manufacture of attenuations shall be thoroughly washed, cleaned and dried after attenuation of a drug. Regular checks shall be carried out on the materials.
(d) The parts of the equipment that come into contact with the attenuation materials shall be of neutral quality and shall not cause any contamination to the material.
(e) Attenuations shall be preserved in properly labeled glass containers.
(f) Alcohol and other vehicles used shall be of Homoeopathic pharmacopoeia specification and shall be free from impurities.
6.3 Trituration: - Trituration technique is used to manufacture drugs from insoluble strains. The procedure / method specified in the Homoeopathic pharmacopoeia shall be adopted.
6.4 Formulations:- Compound formulations shall preferably be in liquid and solid forms and the potency of the ingredients shall be in detectable quantity preferably be in 3x except in case of highly poisonous material and toxins which should not be below 6x. The ingredients shall be compatible to each other. Complete pharmacopoeial name of each ingredient shall be printed on the label along with composition.
6.5 Medicated Insert Pellets: - (a) Pellets shall be manufactured in clean rooms free from particulate contaminants. The equipment used shall enable prevention of contamination and cross- contamination.
(b) The procedures shall be validated.

7. LABORATORY CONTROLS:
Tests as per the pharmacopoeia and requirements shall be carried out on products and materials. The stability of the products shall be established by proper methods. Sterility tests,

wherever applicable, shall be carried out. Control samples shall be preserved for not less than three years after the last sales.

8. PACKINGAND LABELLING:
A minimum area of 50 square meters shall be provided for packing and labeling section.

9. EXPIRYDATE:
Not exceeding sixty (60) months from the date of manufacture.

10. STANDARD OPERATING PRACTICES:
Standard Operating Practices (SOPs) shall be developed for various activities such as receipt, identification, cleaning, drying, warehousing, issue, handling, sampling etc. of all materials. Labels and packing materials shall be examined for correctness and compliance with rules. Records shall be maintained for their printing, use, destruction etc.

11. RECORDSAND REGISTERS:
Records shall be maintained for all the activities. These shall include records of production, records of raw materials, records of testing, records of sales and other supplies, records of rejection, complaints and actions taken, SOPs and records in respect of compliance thereof, log books of equipment, master formula records, records of medical examination and fitness of personnel etc. All records shall be maintained for a period of one year after the expiry of a batch or for three years whichever is later.

[1][SCHEDULE M-II

[*See* Rule 139]

REQUIREMENTS OF FACTORY PREMISES FOR MANUFACTURE OF COSMETICS

I. *GENERAL REQUIREMENTS*

(A) *Location and surroundings*.–The factory shall be located in a sanitary place and hygienic conditions shall be maintained in the premises. Premises shall not be used for residence or be interconnected with residential area. It shall be well ventilated and clean.

(B) *Buildings*.– The buildings used for the factory shall be constructed so as to permit production under hygienic conditions and not to permit entry of insects, rodents, files, etc.

The walls of the room in which manufacturing operations are carried out, shall be up to a height of six feet from the floor, be smooth, waterproof and capable of being kept clean. The flooring shall be smooth, even and washable and shall be such as not to permit retention or accumulation of dust.

(C) *Water supply*: - The water used in manufacture shall be of potable quality.

(D) *Disposal of water*. — Suitable arrangements shall be made for disposal of waste-water.

(E) *Health, clothing and sanitary requirements of the staff*.– All workers shall be free from contagious or infectious diseases. They shall be provided with clean uniforms, masks, headgears, and gloves wherever required. Washing facilities shall also be provided.

(F) *Medical Services*. - Adequate facilities for first aid shall be provided.

(G) Work benches shall be provided for carrying out operations such as filling, labelling, packing, etc. Such benches shall be fitted with smooth, impervious tops capable of being washed.

(H) Adequate facilities shall be provided for washing and drying of glass containers if the same are to be used for packing the product.

II. *REQUIREMENTS OF PLANT AND EQUIPMENT*

The following equipment, area and other requirements are recommended for the manufacture of: –

A. *Powders:*– Face powder, cake make-up, compacts, face packs, masks and rouges, etc.

1. *Equipment:*

(a) Powder mixer of suitable type provided with a dust collector.
(b) Perfume and colour blender.
(c) Sifter with sieves of suitable mesh size.
(d) Ball mill or suitable grinder.

1. Ins. by G.S.R 723(E) , dt. 11-8-1992.

(e) Trays and scoops (stainless steel).
(f) Filling and sealing equipment provided with dust extractor.
(g) For compacts: -
(i) a separate mixer, (ii) compact pressing machine.
(h) Weighing and measuring devices
(i) Storage tanks.

An area of 15 square meters is recommended. The section is to be provided with adequate exhaust fans.

B. Creams, lotions, emulsions, pastes, cleansing milks, shampoos, pomade, brilliantine, shaving creams and hair-oils etc.

(a) Mixing and storage tanks of suitable materials.
(b) Heating kettle – steam, gas or electrically heated.
(c) Suitable agitator.
(d) Colloidal mill or homogeniser (wherever necessary).
(e) Triple roller mill (wherever necessary).
(f) Filling and sealing equipment.
(g) Weighing and measuring devices.

An area of 25 square meters is recommended.

C. Nail Polishes and Nail lacquers.

1. Equipment:

(a) A suitable mixer.
(b) Storage tanks.
(c) Filling machine – hand operated or power driven.
(d) Weighing and Measuring devices.

An area of 15 square meters is recommended. The section shall be provided with flameproof exhaust system.

2. ***Premises:***–The following are the special requirements related to Nail Polishes and Nail Lacquers: -

(a) It shall be situated in an industrial area.
(b) It shall be separate from other cosmetic-manufacturing areas by metal/brick partition up to ceiling.
(c) Floors, walls, ceiling and doors shall be fireproof.
(d) Smoking, cooking and dwelling shall not be permitted and no naked flame shall be brought in the premises.
(e) All electrical wiring and connections shall be concealed and main electric switch shall be outside the manufacturing area.
(f) All equipment, furniture and light fittings in the section shall be flameproof.
(g) Fire extinguisher like foam and dry powder and sufficient number of buckets containing sand shall be provided.
(h) All doors of the section shall open outwards.

3. ***Storage:***

All explosive solvents and ingredients shall be stored in metal cupboards or in a separate enclosed area.

4. ***Manufacture:***

(a) Manufacture of lacquer shall not be undertaken unless the above conditions are complied with.
(b) Workers shall be asked to wear shoes with rubber soles in the section.

5. ***Other requirements:***

No objection certificate from the local Fire Brigade Authorities shall be furnished.

D. Lipsticks and Lip-gloss, etc.

1. Equipment

(a) Vertical mixer.
(b) Jacketted kettle – steam, gas or electrically heated.
(c) Mixing vessel (stainless steel).
(d) Triple roller mill/Ball mill.
(e) Moulds with refrigeration facility.
(f) Weighing and measuring devices.

An area of 15 square meters is recommended.

E. Depilatories.

1. Equipment:

(a) Mixing tanks.
(b) Mixer
(c) Triple roller mill or homogeniser (where necessary).
(d) Filling and sealing equipment.
(e) Weighing and measuring devices.
(f) Moulds (where necessary).

An area of 10 square meters is recommended.

F. ***Preparations used for Eyes***: - Such preparations shall be manufactured under strict hygienic conditions to ensure that these are safe for use.

1. *Eyebrows, Eyelashes, Eyeliners, etc.*

1 *Equipment:*

(a) Mixing tanks.
(b) A suitable mixer.
(c) Homogeniser (where necessary)
(d) Filling and sealing equipment.
(e) Weighing and measuring devices.

An area of 10 square meters is recommended.

2. *Kajal and Surma*

1. *Equipment:*

(a) Base sterilizer.
(b) Powder sterilizer (dry heat oven).
(c) Stainless steel tanks.
(d) A suitable Mixer.

(e) Stainless steel sieves.
(f) Filling and sealing arrangements.
(g) Weighing and measuring devices.
(h) Homogeniser (where necessary).
(i) Pestle and Mortar (for Surma).

An area of 10 square meters with a separate area of 5 square meters for base sterilization is recommended.

Other requirements for 1 and 2:

(a) False ceiling shall be provided wherever required.
(b) Manufacturing area shall be made fly proof. An airlock or an aircurtain shall be provided.
(c) Base used for Kajal shall be sterilized by heating the base at 150 degree C for required time in a separate enclosed area.
(d) The vegetable carbon black powder shall be sterilized in a drying oven at 120 degree C for required time.
(e) All utensils used for manufacture shall be of stainless steel and shall be washed with detergent water, antiseptic liquid and again with distilled water.
(f) Containers employed for 'Kajal' shall be cleaned properly with bactericidal solution and dried.
(g) Workers shall put on clean overalls and use hand gloves wherever necessary.

G. Aerosol.

1. *Equipment:* -

(a) Air-compressor (wherever necessary).
(b) Mixing tanks.
(c) Suitable propellant filling and crimping equipments.
(d) Liquid filling unit.
(e) Leak testing equipment.
(f) Fire extinguisher (wherever necessary)
(g) Suitable filtration equipment.
(h) Weighing and measuring devices.

An area of 15 square meters is recommended.

2. *Other requirements:* - No objection certificate from the Local Fire Brigade Authorities shall be furnished.

H. Alcoholic Fragrance Solutions.

Equipment: -

(a) Mixing tanks with stirrer
(b) Filtering equipment.
(c) Filling and sealing equipment.
(d) Weighing and measuring devices.

An area of 15 square meters is recommended.

I. Hair Dyes.

Equipment:

(a) Stainless steel tanks.
(b) Mixer.

(c) Filling Unit.
(d) Weighing and measuring devices.
(e) Masks, gloves and goggles.

An area of 15 square meters with proper exhaust is recommended.

J. Tooth powders and toothpastes, etc.:

1. *Tooth-powder in General.*

Equipment:

(a) Weighing and measuring devices.
(b) Dry mixer (powder blender).
(c) Stainless steel sieves.
(d) Powder filling and sealing equipments.

An area of 15 square meters with proper exhaust is recommended.

2. *Toothpastes.*

Equipment:

(a) Weighing and measuring devices.
(b) Kettle – steam, gas or electrically heated (where necessary).
(c) Planetary mixer with de-aerator system.
(d) Stainless steel tanks.
(e) Tube filling equipment.
(f) Crimping machine.

An additional area of 15 square meters with proper exhaust is recommended.

3. *Tooth-powder (Black)*

Equipment:

(a) Weighing and measuring devices.
(b) Dry mixer powder blender.
(c) Stainless steel sieves.
(d) Powder filling arrangements.

An area of 15 square meters with proper exhaust is recommended. Areas for manufacturing "Black" and "White" tooth powders should be separate.

K. Toilet Soaps:

Equipment: -

(a) Kettles/pans for saponification.
(b) Boiler or any other suitable heating arrangement.
(c) Suitable stirring arrangement.
(d) Storage tanks or trays.
(e) Driers.
(f) Amalgamator/chipping machine.
(g) Mixer.
(h) Triple roller mill.
(i) Granulator.
(j) Plodder.
(k) Cutter.
(l) Pressing, stamping and embossing machine.
(m) Weighing and measuring devices.

A minimum area of 100 square meters is recommended for the small-scale manufacture of toilet soaps.

The areas recommended above are for basic manufacturing of different categories of cosmetics. In addition to that separate adequate space for storage of raw materials, finished products, packing materials shall be provided in factory premises.[1] [***]

Note No. I–The above requirements of the Schedule are made subject to modification at the discretion of the Licensing Authority, if he is of the opinion that having regard to the nature and extent of the manufacturing operations it is necessary to relax or alter them in the circumstances of a particular case.

Note No. II.–The above requirements do not include requirements of machinery, equipments and premises required for preparation of containers and clousers of different categories of cosmetics. The Licensing Authority shall have the discretion to examine the suitability and adequacy of the machinery, equipments and premises for the purpose of taking into consideration of the requirements of the licensee.

Note No. III.–Schedule M-II specifies equipments and space required for certain categories of cosmetics only. There are other cosmetics items, viz. Attars, perfumes, etc., which are not covered in the above categories. The Licensing Authority shall, in respect of such items or categories of cosmetics have the discretion to examine the adequacy of factory premises, space, plant and machinery and other requisites having regard to the nature and extent of the manufacturing operations involved and direct the licensee to carry on necessary modification in them.

1. The words "A testing laboratory shall also be provided" omitted by G.S.R.285 (E) , dt. 16.7.1996.

[1][SCHEDULE M-III]

[See rules 69, 69A, 75, 75A and 76]

QUALITY MANAGEMENT SYSTEM –FOR NOTIFIED MEDICAL DEVICES AND IN-VITRO DIAGNOSTICS

1. General Requirements:

1.1. This schedule specifies requirements for a quality management system that shall be used by the manufacturer for the design and development, manufacture, packaging, labeling, testing, installation and servicing of medical devices and *in-vitro* diagnostics. If the manufacturer does not carry out design and development activity, the same shall be recorded in the quality management system. The manufacturer shall maintain conformity with this Schedule to reflect the exclusions.

1.2. If any requirement in clause 7(product realisation) of this Schedule is not applicable due to the nature of the medical device and *in-vitro* diagnostics for which the quality management system is applied, the manufacturer does not need to include such a requirement in its quality management system.

1.3. The processes required by this Schedule, which are applicable to the medical device and *in-vitro* diagnostic devices, but which are not performed by the manufacturer are the responsibility of the manufacturer and are accounted for in the manufacturer's quality management system.

1.4. If a manufacturer engages in only some operations subject to the requirements of this part, and not in others, that manufacturer need only to comply with those requirements which are applicable to the operations in which it is engaged.

1.5. It is emphasised that the quality management system requirements specified in this Schedule are in addition to complementary to technical requirements for products.

1.6. Manufacturers of components or parts of finished devices and *in-vitro* diagnostics are encouraged to use appropriate provisions of this regulation as guidance.

2. Applicability:

The provisions of this Schedule shall be applicable to manufacturers of finished devices, In-Vitro Diagnostics, mechanical contraceptives (condoms, intrauterine devices, tubal rings), surgical dressings, surgical bandages, surgical staplers, surgical sutures and ligatures, blood and blood components collection bags with or without anticoagulants intended for human or animal use.

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1. Subs.by G.S.R. 640 (E) , dt. 29.6.2016. Previously, Ins. by G.S.R. 109 (E) , dt. 22.2.1994.

3. Terms and definitions:

3.1 Active implantable medical device.- Active medical device which is intended to be totally or partially introduced, surgically or medically, into the human or animal body or by medical intervention into a natural orifice and which is intended to remain after the procedure.

3.2 Active medical device.- Medical device relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human or animal body or gravity.

3.3 Advisory notice.- Notice issued by the manufacturer, subsequent to delivery of the medical device and *in-vitro* diagnostic devices, to provide supplementary information or to advise what action should be taken in or both in:-

a. the use of a medical device and *in-vitro* diagnostic devices;
b. the modification of a medical device and *in-vitro* diagnostic devices;
c. the return of the medical device and *in-vitro* diagnostic devices to the organization that supplied it; or
d. the destruction of a medical device and *in-vitro* diagnostic devices.

3.4 Customer complaint.- Written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device and *in-vitro* diagnostic devices that has been placed on the market.

3.5 Implantable medical device.- Medical device intended:-

a. to be totally or partially introduced into the human or animal body or a natural orifice; or
b. to replace an epithelial surface or the surface of the eye;

by surgical intervention, and which is intended to remain after the procedure for at least thirty days, and which can only be removed by medical or surgical intervention.

3.6 Component means any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.

3.7 Design input means the physical and performance requirements of a device that are used as a basis for device design.

3.8 Design output means the results of a design effort at each design phase and at the end of the total design effort. The finished design output is the basis for the device master record. The total

finished design output consists of the device, its packaging and labeling, and the device master record.

3.9 Design review means a documented, comprehensive, systematic examination of a design to evaluate the adequacy of the design requirements, to evaluate the capability of the design to meet these requirements, and to identify problems.

3.10 Finished device means any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labeled or sterilized.

3.11 *In-vitro* Diagnostic means *in-vitro* diagnostics referred in this Schedule including diagnostics kits and reagents that fall under sub-clause (i) of clause (b) of section 3 of Drugs and Cosmetics Act, 1940.

3.12 Management with executive responsibility means those senior employees of a manufacturer who have the authority to establish or make changes to the manufacturer's quality policy and quality system.

3.13 Medical device referred in this Schedule means devices that are notified under clause (iv) of sub-section (b) of section 3 of Drugs and Cosmetics Act, 1940.

3.14 Quality audit means a systematic, independent examination of a manufacturer's quality system that is performed at defined intervals and at sufficient frequency to determine whether both quality system activities and the results of such activities comply with quality system procedures, that these procedures are implemented effectively, and that these procedures are suitable to achieve quality system objectives.

3.15 Quality policy means the overall intention and direction of an organization with respect to quality, as established by management with executive responsibility.

3.16 Quality system means the organisational structure, responsibilities, procedures, processes, and resources for implementing quality management.

3.17 Rework means action taken on a nonconforming product that will fulfill the specified Device Master File requirements before it is released for distribution.

3.18 Specification means any requirement with which a product, process, service, or other activity must conform.

3.19 Validation means confirmation by examination and provision of objective evidence that the particular requirement for a specific intended use can be consistently fulfilled;

3.19.1 Process validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

3.19.2 Design validation means establishing by objective evidence that device specifications conform with user needs and intended use(s).

3.20 Verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

4 Quality management system.-

4.1 General:

The manufacturer shall establish, document, implement and maintain a quality management system and maintain its effectiveness in accordance with the requirements of this schedule.

The manufacturer shall;-

(a) identify the processes needed for the quality management system and their application throughout the organization;

(b) determine the sequence and interaction of these processes;

(c) determine criteria and methods needed to ensure that both the operation and control of these processes are effective;

(d) ensure the availability of resources and information necessary to support the operation and monitoring of these processes;

(e) monitor, measure and analyse these processes; and

(f) implement actions necessary to achieve planned results and maintain the effectiveness of these processes.

These processes shall be managed by the manufacturer in accordance with the requirements of this Schedule. Where a manufacturer chooses to outsource any process that affects product conformity with requirements, the manufacturer shall ensure control over such processes. Control of such outsourced processes shall be identified within the quality management system.

NOTE: Processes needed for the quality management system referred to above shall include processes for management activities, provision of resources, product realization and measurement.

4.2 Documentation requirements.-

4.2.1 General

The quality management system documentation shall include;-

(a) documented statements of a quality policy and quality objectives;

(b) a quality manual;

(c) documented procedures required by this schedule;

(d) documents needed by the manufacturer to ensure the effective planning, operation and control of its processes;

(e) records required by this schedule, and

where this schedule specifies that a requirement, procedure, activity or special arrangement be "documented", it shall, in addition, be implemented and maintained.

For each type or model of medical device or *In-vitro* Diagnostics, the manufacturer shall establish and maintain a file either containing or identifying documents defining product specifications and quality management system requirements. These documents shall define the complete manufacturing process and, if applicable, installation.

The manufacture shall prepare documentation for device or *in-vitro* diagnostics in a form of a Device Master File containing specific information as referred to in Annexure-A appended to this Schedule.

Data may be recorded by electronic data processing systems or other reliable means, but documents and record relating to the system in use shall also be available in a hard copy to facilitate checking of the accuracy of the records. Wherever documentation is handled by electronic data processing methods, authorized persons shall enter or modify data in the computer. There shall be record of changes and deletions. Access shall be restricted by 'passwords' or other means and the result of entry of critical data shall be independently checked. Batch records electronically stored shall be protected by a suitable back-up. During the period of retention, all relevant data shall be readily available.

4.2.2 Quality manual.-

The manufacturer shall establish and maintain a quality manual that includes:-

(a) the scope of the quality management system, including details of and justification for any exclusion or non-application or both;

(b) the documented procedures established for the quality management system, or reference to them; and

(c) a description of the interaction between the processes of the quality management system.

The quality manual shall outline the structure of the documentation used in the quality management system.

The manufacturer shall prepare documentation in a form of a Plant Master File containing specific information about the facilities, personnel and other details as prescribed in Annexure B appended to this Schedule.

4.2.3 Control of documents.-

Documents required by the quality management system shall be controlled. Records are a special type of document and shall be controlled according to the requirements given in the control of records. Documents shall be approved, signed and dated by the appropriate and the authorised person.

A documented procedure shall be established to define the controls needed.-

(a) to review and approve documents for adequacy prior to issue;
(b) to review and update as necessary and re-approve documents;
(c) to ensure that changes and the current revision status of documents are identified;
(d) to ensure that relevant versions of applicable documents are available at points of use;
(e) to ensure that documents remain legible and readily identifiable;
(f) to ensure that documents of external origin are identified and their distribution controlled; and
(g) to prevent the unintended use of obsolete documents, and to apply suitable identification to them if they are retained for any purpose.

Changes to document shall be reviewed and approved. Change records shall be maintained which will include a description of the change, identification of the affected documents, the signature of the approving individual, the approval date, and when the change becomes effective.
The manufacturer shall ensure that changes to documents are reviewed and approved either by the original approving functionary or another designated functionary which has access to pertinent background information upon which to base its decisions.

The manufacturer shall define the period for which at least one copy of obsolete controlled documents shall be retained. This period shall ensure that documents to which medical devices or *in-vitro* diagnostics have been manufactured and tested are retained for at least one year after the date of expiry of the medical device or *in-vitro* diagnostic as defined by the manufacturer.

4.2.4 Control of records.-

Records shall be established and maintained to provide evidence of conformity to the requirements and of the effective operation of the quality management system. Records shall remain legible, readily identifiable and retrievable. A documented procedure shall be established to define the

controls needed for the identification, storage, protection, retrieval, retention time and disposition of records.

The manufacturer shall retain the records for a period of time at least one year after the date of expiry of the medical device or *in-vitro* diagnostics as defined by the manufacturer, but not less than two years from the date of product release by the manufacturer.

5 Management responsibility.-

5.1 Management commitment:

Top management of the manufacturer shall provide evidence of its commitment to the development and implementation of the quality management system and maintaining its effectiveness by:-

(a) communicating to the employees the importance of meeting customer as well as statutory and regulatory requirements;
(b) establishing the quality policy;
(c) ensuring that quality objectives are established;
(d) conducting management reviews; and
(e) ensuring the availability of resources.

5.2 Customer focus:

Top management of the manufacturer shall ensure that customer requirements are determined and are met.

5.3 Quality policy:

Top management of the manufacturer shall ensure that the quality policy:-

(a) is appropriate to the purpose of the manufacturing facility;
(b) includes a commitment to comply with requirements and to maintain the effectiveness of the quality management system;
(c) provides a framework for establishing and reviewing quality objectives;
(d) is communicated and understood within the manufacturer's organization; and
(e) is reviewed for continuing suitability.

5.4 Planning.-

5.4.1 Quality objectives:

Top management of the manufacturer shall ensure that quality objectives, including those needed to meet requirements for product, are established at relevant functions and levels within the manufacturing organization. The quality objectives shall be measurable and consistent with the quality policy.

5.4.2 Quality management system planning:

Top management of the manufacturer shall ensure that.-

(a) the planning of the quality management system is carried out in order to meet the specified requirements, as well as the quality objectives; and

(b) the integrity of the quality management system is maintained when changes to the quality management system are planned and implemented.

5.5 Responsibility, authority and communication.-

5.5.1 Responsibility and authority:

Top management of the manufacturer shall ensure that responsibilities and authorities are defined, documented and communicated within the manufacturing organisation.

Top management of the manufacturer shall establish the interrelation of all personnel who manage, perform and verify work affecting quality, and shall ensure the independence and authority necessary to perform these tasks.

5.5.2 Management representative:

Top management shall appoint a member of management who, irrespective of other responsibilities, shall have responsibility and authority that includes:-

(a) ensuring that processes needed for the quality management system are established, implemented and maintained;

(b) reporting to top management on the performance of the quality management system and any need for improvement; and

(c) ensuring the promotion of awareness of regulatory and customer requirements throughout the manufacturing organization.

5.5.3 Internal communication:

Top management shall ensure that appropriate communication processes are established within the Manufacturing organization and that communication takes place regarding the effectiveness of the quality management system.

5.6 Management review.-

5.6.1 General:

Top management shall review the organization's quality management system, at planned intervals, to ensure its continuing suitability, adequacy and effectiveness. This review shall include assessing opportunities for improvement and the need for changes to the quality management system, including the quality policy and quality objectives. Records from management reviews shall be maintained.

5.6.2 Review input:

The input to management review shall include information on:-

(a) results of audits,

(b) customer feedback,

(c) process performance and product conformity,

(d) status of preventive and corrective actions,

(e) follow-up actions from previous management reviews,

(f) changes that could affect the quality management system,

(g) recommendations for improvement, and

(h) new or revised regulatory requirements as and when issued.

5.6.3 Review output:

The output from the management review shall include any decisions and actions related to:-

(a) improvements needed to maintain the effectiveness of the quality management system and its processes,

(b) improvement of product related to customer requirements, and

(c) resource needs.

6 Resource management.-

6.1 Provision of resources:

The manufacturing organization shall determine and provide the resources needed

(a) to implement the quality management system and to maintain its effectiveness, and

(b) to meet regulatory and customer requirements.

6.2 Human resources.-

6.2.1 General:

Personnel performing work affecting product quality shall be competent on the basis of appropriate education, training, skills and experience. Number of personnel employed shall be adequate and in direct proportion to the workload. Prior to employment, all personnel, shall undergo medical examination including eye examination, and shall be free from communicable or contagious diseases. Thereafter, they should be medically examined periodically, at least once a year. Records shall be maintained thereof.

6.2.2 Competence, awareness and training:

The manufacturer shall:-

(a) determine the necessary competence for personnel performing work affecting product quality,

(b) provide training or take other actions to satisfy these needs,

(c) evaluate the effectiveness of the actions taken,

(d) ensure that its personnel are aware of the relevance and importance of their activities and how they contribute to the achievement of the quality objectives,

(e) maintain appropriate records of education, training, skills and experience, and

(f) establish documented procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities.

6.3 Infrastructure:

The organisation shall determine, provide and maintain the infrastructure needed to achieve conformity to product requirements. Infrastructure includes, as applicable:-

(a) buildings, workspace and associated utilities.

(b) process equipment (both hardware and software), and

(c) supporting services (such as transport or communication).

The manufacturer shall establish documented requirements for maintenance activities, including their frequency, when such activities or lack thereof can affect product quality. Records of such maintenance shall be maintained.

6.4 Work environment:

The organisation shall determine and manage the work environment needed to achieve conformity to product requirements. The following requirements shall apply, namely:-

(a) the manufacturer shall establish documented requirements for health, cleanliness and clothing of personnel if contact between such personnel and the product or work environment could adversely affect the quality of the product;

(b) if work environment conditions can have an adverse effect on product quality, the manufacturer shall establish documented requirements as per **Annexure-C** of this schedule for the work environment conditions and documented procedures or work instructions to monitor and control these work environment condition;

(c) the manufacturer shall ensure that all personnel who are required to work temporarily under special environmental conditions within the work environment are appropriately trained and supervised by a trained person;

(d) if appropriate, special arrangements shall be established and documented for the control of contaminated or potentially contaminated product in order to prevent contamination of other product, the work environment or personnel.

(e) all personnel shall bear clean body covering appropriate to their duties. Smoking, eating, drinking, chewing or keeping food and drink shall not be permitted in production, laboratory and storage areas.

7 Product realisation.-

7.1 Planning of product realization:

The manufacturer shall plan and develop the processes needed for product realization. Planning of product realization shall be consistent with the requirements of the other processes of the quality management system.

In planning product realisation, the manufacturer shall determine the following, as appropriate:-

(a) quality objectives and requirements for the product;

(b) the need to establish processes, documents, and provide resources specific to the product;

(c) required verification, validation, monitoring, inspection and test activities specific to the product and the criteria for product acceptance;

(d) records needed to provide evidence that the realisation processes and resulting product meet requirements.

The output of this planning shall be in a form suitable for the manufacturer's method of operations.

The manufacturer organisation shall establish documented requirements for risk management (as per the IS or ISO 14971) throughout product realisation. Records arising from risk management shall be maintained.

7.2 Customer-related processes.-

7.2.1 Determination of requirements related to the product:

The manufacturer shall determine:-

(a) requirements specified by the customer, including the requirements for delivery and post-delivery activities,

(b) requirements not stated by the customer but necessary for specified or intended use, where known;

(c) statutory requirements related to the product, and

(d) any additional requirements determined by the manufacturer.

7.2.2 Review of requirements related to the product:

The manufacturer shall review the requirements related to the product. This review shall be conducted prior to the manufacturer's commitment to supply a product to the customer and shall ensure that:-

(a) product requirements are defined and documented;

(b) contract or order requirements differing from those previously expressed are resolved; and

(c) the manufacturer has the ability to meet the defined requirements.

Records of the results of the review and actions arising from the review shall be maintained.

Where the customer provides no documented statement of requirement, the customer requirements shall be confirmed by the manufacturer before acceptance.

Where product requirements are changed, the manufacturer shall ensure that relevant documents are amended and that relevant personnel are made aware of the changed requirements.

7.2.3 Customer communication:

The manufacturer shall determine and implement effective arrangements for communicating with customers in relation to:-

(a) product information;

(b) enquiries, contracts or order handling, including amendments;

(c) customer feedback, including customer complaints; and

(d) advisory notices.

7.3 Design and development.-

7.3.1 Design and development planning:

The manufacturer shall establish documented procedures for design and development. The manufacturer shall plan and control the design and development of product. During the design and development planning, the manufacturer shall determine :-

(a) the design and development stages;

(b) the review, verification, validation and design transfer activities that are appropriate at each design and development stage; and

(c) the responsibilities and authorities for design and development.

The manufacturer shall manage the interfaces between different groups involved in design and development to ensure effective communication and clear assignment of responsibility.

Planning output shall be documented, and updated as appropriate, as the design and development progresses.

NOTE: Design transfer activities during the design and development process ensure that design and development outputs are verified as suitable for manufacturing before becoming final production specifications.

7.3.2 Design and development inputs:

Inputs relating to product requirements shall be determined and records maintained. The design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patients.

These inputs shall include:-

(a) functional, performance and safety requirements, according to the intended use;

(b) applicable statutory and regulatory requirements;

(c) where applicable, information derived from previous similar designs;

(d) other requirements essential for design and development; and

(e) output(s) of risk management.

These inputs shall be reviewed for adequacy and approved by designated individual.
Requirements shall be complete, unambiguous and not in conflict with each other.

7.3.3 Design and development outputs:

The outputs of design and development shall be provided in a form that enables verification against the design and development input and shall be documented, reviewed, and approved prior to release.

Design and development outputs shall:-

(a) meet the input requirements for design and development;

(b) provide appropriate information for purchasing, production and for service provision;

(c) contain or reference product acceptance criteria; and

(d) specify the characteristics of the product that are essential for its safe and proper use.

Records of the design and development outputs shall be maintained.
Records of design and development outputs can include specifications, manufacturing procedures, engineering drawings, and engineering or research logbooks.

7.3.4 Design and development review:

At suitable stages, systematic reviews of design and development shall be performed in accordance with planned arrangements:-

(a) to evaluate the ability of the results of design and development to meet requirements; and

(b) to identify any problems and propose necessary actions.

Participants in such reviews shall include representatives of functions concerned with the design and development stage being reviewed, as well as other specialist personnel.
Records of the results of the reviews and any necessary actions shall be maintained

7.3.5 Design and development verification:

Verification shall be performed in accordance with planned arrangements to ensure that the design and development outputs have met the design and development input requirements. Records of the results of the verification and any necessary actions shall be maintained.

7.3.6 Design and development validation:

Design and development validation shall be performed in accordance with planned arrangements to ensure that the resulting product is capable of meeting the requirements for the specified application or intended use.

Design validation shall be performed under defined operating conditions on initial production units, lots, or batches or their equivalence. Design validation shall include software validation and risk analysis, where appropriate validation shall be completed prior to the delivery or implementation of the product.

Records of the results of validation and any necessary actions shall be maintained.

As part of design and development validation, the manufacturer shall perform clinical evaluations and/or evaluation of performance of the medical device or *In-vitro* Diagnostics.

NOTE 1.- If a medical device or *In-vitro* Diagnostic can only be validated following assembly and installation at point of use, delivery is not considered to be complete until the product has been formally transferred to the customer.

NOTE 2.- Provision of the medical device for purposes of clinical evaluations and/or evaluation of performance is not considered to be delivery.

7.3.7 Control of design and development changes:

Design and development changes shall be identified and records maintained. The changes shall be reviewed, verified and validated, as appropriate, and approved before implementation. The review of design and development changes shall include evaluation of the effect of the changes on constituent parts and product already delivered. Records of the results of the review of changes and any necessary actions shall be maintained.

Note.-Each manufacturer shall establish and maintain a Design History File for each type of device. The Design History File shall contain or reference the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of design and development.

7.4 Purchasing.-

7.4.1 Purchasing process:

The manufacturer organisation shall establish documented procedures to ensure that purchased product conforms to specified purchase requirements. The type and extent of control applied to the supplier and the purchased product shall be dependent upon the effect of the purchased product on subsequent product realisation or the final product.

The manufacturer shall evaluate and select suppliers based on their ability to supply product in accordance with the manufacturer's requirements. Criteria for selection, evaluation and re-evaluation shall be established.

Records of the results of evaluations and any necessary actions arising from the evaluation shall be maintained.

7.4.2 Purchasing information:

Purchasing information shall describe the product to be purchased, including where appropriate:-

(a) requirements for approval of product, procedures, processes and equipment;

(b) requirements for qualification of personnel; and

(c) quality management system requirements.

The manufacturer shall ensure the adequacy of specified purchase requirements prior to their communication to the supplier.

To the extent required for traceability, the manufacturer shall maintain documents and records of relevant purchasing information.

7.4.3 Verification of purchased product:

The manufacturer shall establish and implement the inspection or other activities necessary for ensuring that purchased product meets specified purchase requirements. Where the manufacturer intends to perform verification at the supplier's premises, the manufacturer shall state the intended verification arrangements and method of product release in the purchasing information. Records of the verification shall be maintained.

7.5 Production and service provision.-

7.5.1 Control of production and service provision:

7.5.1.1 General requirements:

The manufacturer shall plan and carry out production and service provision under controlled conditions. Controlled conditions shall include, as applicable:-

(a) the availability of information that describes the characteristics of the product,

(b) the availability of documented procedures, documented requirements, work instructions; and reference materials and reference measurement procedures as necessary;

(c) the use of suitable equipment;

(d) the availability and use of monitoring and measuring devices;

(e) the implementation of monitoring and measurement;

(f) the implementation of release, delivery and post-delivery activities; and

(g) the implementation of defined operations for labeling and packaging.

The manufacturer shall establish and maintain a record for each batch of medical device or *In-vitro* Diagnostic devices that provides traceability and identifies the amount manufactured and amount approved for distribution. The batch record shall be verified and approved.

7.5.1.2 Control of production and service provision — Specific requirements

7.5.1.2.1 Cleanliness of product and contamination control:

The manufacturer shall establish documented requirements for cleanliness of product if:-

(a) product is cleaned by the manufacturer prior to sterilisation or its use; or

(b) product is supplied non-sterile to be subjected to a cleaning process prior to sterilisation or its use; or

(c) product is supplied to be used non-sterile and its cleanliness is of significance in use; or

(d) process agents are to be removed from product during manufacture.

If the product is cleaned in accordance with (a) or (b) above, the requirements content in clause 6.4 (a) and (b) do not apply prior to the cleaning process

7.5.1.2.2 Installation activities:

If appropriate, the manufacturer shall establish documented requirements which contain acceptance criteria for installing and verifying the installation of the medical device or *In-vitro* Diagnostic device.

If the agreed customer requirements allow installation to be performed other than by manufacturer or its authorised agent, the manufacturer shall provide documented requirements for installation and verification. Records of installation and verification performed by the manufacturer or its authorized agent shall be maintained.

7.5.1.3 Particular requirements for sterile medical devices:

The manufacturer shall maintain records of the process parameters for the sterilisation process which was used for each sterilisation batch. Sterilisation records shall be traceable to each production batch of medical device.

7.5.2 Validation of processes for production and service provision.-

7.5.2.1 General:

The manufacturer shall validate any processes for production and service provision where the resulting output cannot be verified by subsequent monitoring or measurement. This includes any processes where deficiencies become apparent only after the product is in use. Validation shall demonstrate the ability of these processes to achieve planned results.

The manufacturer shall establish arrangements for these processes including, as applicable:-

(a) defined criteria for review and approval of the processes;

(b) approval of equipment and qualification of personnel

(c) use of specific methods and procedures,;

(d) requirements for records; and

(e) revalidation.

The manufacturer shall establish documented procedures for the validation of the application of computer software (and its changes to such software or its application) for production and service provision that affect the ability of the product conform to specified requirements. Such software applications shall be validated prior to initial use.

Records of validation shall be maintained.

7.5.2.2 Particular requirements for sterile medical devices:

The manufacturer shall establish documented procedures for the validation of sterilization processes. Sterilisation processes shall be validated prior to initial use. The records of validation of each sterilisation process shall be maintained.

7.5.3 Identification and traceability.-

7.5.3.1 Identification:

The manufacturer shall identify the product by suitable means throughout product realization, and shall establish documented procedures for such product identification. The manufacturer shall establish documented procedures to ensure that medical devices and *In-vitro* Diagnostics returned to the manufacturer are identified and distinguished from conforming product.

7.5.3.2 Traceability.-

7.5.3.2.1 General:

The manufacturer shall establish documented procedures for traceability. Such procedures shall define the extent of product traceability and the records required.

Where traceability is a requirement, the manufacturer shall control and record the unique identification of the product.

NOTE.- Configuration management is a means by which identification and traceability can be maintained.

7.5.3.2.2 Particular requirements for active implantable medical devices and implantable medical devices:

In defining the records required for traceability, the manufacturer shall include records of all components, materials and work environment conditions, if these could cause the medical device not to satisfy its specified requirements.

The manufacturer shall require that its agents or distributors maintain records of the distribution of active implantable medical devices and implantable medical devices to allow traceability and that such records are available for inspection. Records of the name and address of the shipping package consignee shall be maintained.

7.5.3.3 Status identification:

The manufacturer shall identify the product status with respect to monitoring and measurement requirements. The identification of product status shall be maintained throughout production, storage, implant, usage and installation of the product to ensure that only product that has passed the required inspections and tests (or released under an authorized concession) is dispatched, used or installed.

7.5.4 Customer property:

The manufacturer shall exercise care with customer property while it is under the manufacturer's control or being used by the manufacturer. The manufacturer shall identify, verify, protect and safeguard customer property provided for use or incorporation into the product. If any customer property is lost, damaged or otherwise found to be unsuitable for use, this shall be reported to the customer and records maintained.

NOTE.- Customer property can include intellectual property or confidential health information.

7.5.5 Preservation of product:

The manufacturer shall establish documented procedures or documented work instructions for preserving the conformity of product during internal processing and delivery to the intended destination. This preservation shall include identification, handling, packaging, storage and protection. Preservation shall also apply to the constituent parts of a product.

The manufacturer shall establish documented procedures or documented work instructions for the control of product with a limited shelf-life or requiring special storage conditions. Such special storage conditions shall be controlled and recorded.

7.6 Control of monitoring and measuring devices:

The manufacturer shall determine the monitoring and measurement to be undertaken and the monitoring and measuring devices needed to provide evidence of conformity of product to determined requirements.

The manufacturer shall establish documented procedures to ensure that monitoring and measurement can be carried out and are carried out in a manner that is consistent with the monitoring and measurement requirements.

Where necessary to ensure valid results, measuring equipment shall be:-

(a) calibrated or verified at specified intervals, or prior to use, against measurement standards traceable to Bureau of Indian Standards wherever available ; where no such standards exist, the basis used for calibration or verification shall be recorded;

(b) adjusted or re-adjusted as necessary;

(c) identified to enable the calibration status to be determined;

(d) safeguarded from adjustments that would invalidate the measurement result;

(e) protected from damage and deterioration during handling, maintenance and storage.

In addition, the manufacturer shall assess and record the validity of the previous measuring results when the equipment is found not to conform to requirements. The manufacturer shall take appropriate action on the equipment and any product affected. Records of the results of calibration and verification shall be maintained.

When used in the monitoring and measurement of specified requirements, the ability of computer software to satisfy the intended application shall be confirmed. This shall be undertaken prior to initial use and reconfirmed as necessary.

8 Measurement, analysis and improvement.-

8.1 General:

The manufacturer shall plan and implement the monitoring, measurement, analysis and improvement processes needed:-

(a) to demonstrate conformity of the product;

(b) to ensure conformity of the quality management system; and

(c) to maintain the effectiveness of the quality management system.

This shall include determination of applicable methods, including statistical techniques, and the extent of their use.

Note.- If relevant Indian standards are not available, International standards are applicable. In case no Indian or International standards are available, validated testing process of the manufacturer is applicable.

8.2 Monitoring and measurement.-

8.2.1 Feedback:

As one of the measurements of the performance of the quality management system, the manufacturer shall monitor information relating to whether the manufacturer has met customer or regulatory requirements. The methods for obtaining and using this information shall be determined.

The manufacturer shall establish a documented procedure for a feedback system to provide early warning of quality problems and for input into the corrective and preventive action processes.

8.2.2 Internal audit:

The manufacturer shall conduct internal audits at planned intervals to determine whether the quality management system:-

a) conforms to the planned arrangements, to the requirements of this schedule and to the quality management system requirements established by the manufacturer, and

b) is effectively implemented and maintained.

An audit programme shall be planned, taking into consideration the status and importance of the processes and areas to be audited, as well as the results of previous audits. The audit criteria, scope, frequency and methods shall be defined. Selection of auditors and conduct of audits shall ensure objectivity and impartiality of the audit process. Auditors shall not audit their own work.

The responsibilities and requirements for planning and conducting audits, and for reporting results and maintaining records shall be defined in a documented procedure. The management responsible for the area being audited shall ensure that actions are taken without undue delay to eliminate detected nonconformities and their causes. Follow-up activities shall include the verification of the actions taken and the reporting of verification results.

8.2.3 Monitoring and measurement of processes:

The manufacturer shall apply suitable methods for monitoring and, where applicable, measurement of the quality management system processes. These methods shall demonstrate the ability of the processes to achieve planned results. When planned results are not achieved, correction and corrective action shall be taken, as appropriate, to ensure conformity of the product.

8.2.4 Monitoring and measurement of product.-

8.2.4.1 General requirements:

The manufacturer shall monitor and measure the characteristics of the product to verify that product requirements have been met. This shall be carried out at appropriate stages of the product realisation process in accordance with the planned arrangements and documented procedures.

Evidence of conformity with the acceptance criteria shall be maintained. Records shall indicate the person(s) authorizing release of product. Product release shall not proceed until the planned arrangements have been satisfactorily completed.

8.2.4.2 Particular requirement for active implantable medical devices and implantable medical Devices wherever applicable:

The manufacturer shall record the identity of personnel performing any inspection or testing.

8.3 Control of nonconforming product

The manufacturer shall ensure that product which does not conform to product requirements is identified and controlled to prevent its unintended use or delivery. The controls and related responsibilities and authorities for dealing with nonconforming product shall be defined in a documented procedure.

The manufacturer shall deal with nonconforming product by one or more of the following ways:

(a) by taking action to eliminate the detected nonconformity;

(b) by authorizing its use, release or acceptance under concession;

(c) by taking action to preclude its original intended use or application.

The manufacturer shall ensure that nonconforming product is accepted by concession only if regulatory requirements are met. Records of the identity of the person authorisng the concession shall be maintained.

Records of the nature of nonconformities and any subsequent actions taken, including concessions obtained, shall be maintained.

When nonconforming product is corrected it shall be subject to re-verification to demonstrate conformity to the requirements. When nonconforming product is detected after delivery or use has started, the manufacturer shall take action appropriate to the effects, or potential effects, of the non-conformity.

If product needs to be reworked (one or more times), the manufacturer shall document the rework process in a work instruction that has undergone the same authorisation and approval procedure as the original work instruction. Prior to authorisation and approval of the work instruction, a determination of any adverse effect of the rework upon product shall be made and documented.

8.4 Analysis of data:

The manufacturer shall establish documented procedures to determine, collect and analyze appropriate data to demonstrate the suitability and effectiveness of the quality management system and to evaluate whether improvement of the effectiveness of the quality management system can be made.

This shall include data generated as a result of monitoring and measurement and from other relevant sources.

The analysis of data shall provide information relating to:-

(a) feedback

(b) conformity to product requirements;

(c) characteristics and trends of processes and products including opportunities for preventive action; and

(d) suppliers.

Records of the results of the analysis of data shall be maintained.

8.5 Improvement.-

8.5.1 General:

The manufacturer shall identify and implement any changes necessary to ensure and maintain the continued suitability and effectiveness of the quality management system through the use of the quality policy, quality objectives, audit results, analysis of data, corrective and preventive actions and management review.

The manufacturer shall establish documented procedures for the issue and implementation of advisory notices. These procedures shall be capable of being implemented at any time. Records of all customer complaint investigations shall be maintained. If investigation determine that the activities outside the manufacturer's organisation contributed to the customer complaint, relevant information shall be exchanged between the organisations involved.

If any customer complaint is not followed by corrective or preventive action, the reason shall be recorded and approved. Manufacturer shall notify the adverse event to the regulatory authority and establish documented procedures for the same.

8.5.2 Corrective action:

The manufacturer shall take action to eliminate the cause of nonconformities in order to prevent recurrence. Corrective actions shall be appropriate to the effects of the nonconformities encountered. A documented procedure shall be established to define requirements for:-

(a) reviewing nonconformities (including customer complaints);
(b) determining the causes of nonconformities;
(c) evaluating the need for action to ensure that nonconformities do not recur
(d) determining and implementing action needed, including, if appropriate, updating documentation;
(e) recording of the results of any investigation and of action taken; and
(f) reviewing the corrective action taken and its effectiveness.

8.5.3 Preventive action:

The manufacturer shall determine action to eliminate the causes of potential nonconformities in order to prevent their occurrence. Preventive actions shall be appropriate to the effects of the potential problems. A documented procedure shall be established to define requirements for

(a) determining potential nonconformities and their causes,
(b) evaluating the need for action to prevent occurrence of nonconformities,
(c) determining and implementing action needed,
(d) recording of the results of any investigations and of action taken, and
(e) reviewing preventive action taken and its effectiveness.

Annexure 'A'

(refer para 4.2.1)

The manufacturer shall prepare a succinct document in the form of Device Master File containing specific information about the device manufacturing in the premises.

1.0 Executive Summary:

An executive summary shall be provided by the manufacturer and shall contain:

Introductory descriptive information on the medical device or *In-vitro* Diagnostics, the intended use and indication for use, Class of Device, novel features of the device (if any), shelf life of the device and a synopsis on the content of the dossier information regarding sterilisation of the device (whether it is sterile or non-sterile; if sterile, mode of sterilisation)

2.0 Device Description And Product Specification, Including Variants And Accessories:

2.1 Device Description

2.2 Product Specification

2.3 Reference to predicate and/or previous generations of the device

3.0 Labelling

4.0 Design And Manufacturing Information:

4.1 Device Design

4.2 Manufacturing Processes

5.0 Essential Principles (EP) Checklist

6.0 Risk Analysis And Control Summary

7.0 Product Verification And Validation:

7.1 Biocompatibility

7.2 Medicinal Substances

7.3 Biological Safety

7.4 Sterilisation

7.5 Software Verification and Validation

7.6 Animal Studies

7.7 Shelf Life/Stability Data

7.8 Clinical Evidence

7.9 Post Marketing Surveillance Data (Vigilance Reporting)

8. Additional information in case of the diagnostic kits:

Product dossier showing the:

8.1 The details of source antigen or antibody as the case may be and characterization of the same.

Process control of coating of antigen or antibody on the base material like Nitrocellulose paper, strips or cards or enzyme-linked immunosorbent assay (ELISA) wells etc.

Detailed composition of the kit and manufacturing flow chart process of the kit showing the specific flow diagram of individual components or source of the individual components.

8.2 Test protocol of the kit showing the specifications and method of testing. In house evaluation report of sensitivity, specificity and stability studies.

8.3 The detailed test report of all the components used/packed in the finished kit.

8.4 Pack size and labelling.

8.5 Product inserts.

Specific evaluation report, if done by any laboratory in India, showing the sensitivity and specificity of the kit.

Specific processing like safe handling, material control, area control, process control, and stability studies, storage at quarantine stage and finished stage, packaging should be highlighted in the product dossier.

Annexure `B`

(refer para 4.2.2)

The manufacturer shall prepare a succinct document in the form of Plant Master File containing specific information about the production and/or control of device manufacturing carried out at the premises. It shall contain the following information:

1. General Information:

(i) brief information on the site (including name and address), relation to other sites;

(ii) manufacturing activities;

(iii) any other operations carried out on the site

(iv) name and exact address of the site, including telephone, fax numbers, web site URL and e-mail address;

(v) type of medical devices handled on the site and information about specifically toxic or hazardous substances handled, mentioning the way they are handled and precautions taken;

(vi) short description of the site (size, location and immediate environment and other activities on the site);

(vii) number of employees engaged in Production, Quality Control, warehousing, and distribution;

(viii) use of outside scientific, analytical or other technical assistance in relation to the design, manufacture and testing;

(ix) short description of the quality management system of the company;

(x) devices details registered with foreign countries;

2. Personnel:

(i) organisation chart showing the arrangements for key personne;l

(ii) qualifications, experience and responsibilities of key personnel;

(iii) outline of arrangements for basic and in-service training and how records are maintained;

(iv) health requirements for personnel engaged in production

(v) personnel hygiene requirements, including clothing.

3. Premises and Facilities:

(i) layout of premises with indication of scale;

(ii) nature of construction, finishes/fixtures and fittings;

(iii) brief description of ventilation systems. More details should be given for critical areas with potential risks of airborne contamination (including schematic drawings of the systems). Classification of the rooms used for the manufacture of sterile products should be mentioned;

(iv) special areas for the handling of highly toxic, hazardous and sensitizing materials;

(v) brief description of water systems (schematic drawings of the systems are desirable) including sanitation;

(vi) maintenance (description of planned preventive maintenance programmes for premises and recording system);

4. Equipment:

(i) Brief description of major production and quality control laboratories equipment (a list of the equipment is required);

(ii) maintenance (description of planned preventive maintenance programmes and recording system);

(iii) qualification and calibration, including the recording system. Arrangements for computerized systems validation.

5. Sanitation:

Availability of written specifications and procedures for cleaning the manufacturing areas and equipments.

6. Production:

(i) Brief description of production operations using, wherever possible, flow sheets and charts specifying important parameters ;

(ii) arrangements for the handling of starting materials, packaging materials, bulk and finished products, including sampling, quarantine, release and storage;

(iii) arrangements for reprocessing or rework;

(iv) arrangements for the handling of rejected materials and products;

(v) brief description of general policy for process validation.

7. Quality Assurance:

Description of the Quality Assurance system and of the activities of the Quality Assurance Department. Procedures for the release of finished products.

8. Storage:

Policy on the storage of medical device.

9. Documentation:

Arrangements for the preparation, revision and distribution of necessary documentation, including storage of master documents.

10. Medical Device Complaints and Field Safety Corrective Action:

(i) Arrangements for the handling of complaints ;

(ii) Arrangements for the handling of field safety corrective action

11. Internal Audit:

Short Description of the internal audit system.

12. Contract Activities:

Description of the way in which the compliance of the contract acceptor is assessed.

Annexure 'C'

Environmental requirement for Notified medical devices and *in-vitro* diagnostics

Name of Device	Type of Operation	ISO Class (At rest)
Cardiac stent/Drug Eluting Stent	Primary Packing and Crimping	5
	Washing, Ultrasonic cleaning &Drug coating	7
	Assembly, Wrapping & Packaging	8
	Laser cutting, Descaling, Annealing & Electro polishing	9
Heart Valves	Valve Packing	5
	Ultrasonic Cleaning & Visual Inspection	7
	Frame & Disc Assembly	7
Intra Ocular Lenses	Packing & Sealing	5
	Final Inspection	7
	Power Checking& Final Cleaning	8
	Tumble Polishing & Lathe Cutting	9
Bone Cements	Final Product Filling	5
	Sieving & Calcinations	7
	Powder Preparation, Granulation &Drying	8
Internal Prosthetic Replacement	Packing	5
	Product Preparation	7
	Component Preparation	8
Orthopedic Implants	Polishing &Cleaning & packaging (to be sterilized in factory premises)	7
	Polishing , cleaning & packaging (Non Sterile- to be sterilized in Hospital)	8
	Cutting, lathing	9
Catheters /Ablation Device / I V Cannulae / Scalp Vein Set/ Hypodermic Syringes/ Hypodermic Needles / Perfusion Sets	Assembly, Coating, Wrapping & Packing	7
	Component Preparation & Cleaning	8
	Moulding	9
Condom	Compounding	Well ventilated area with minimum 5 micron filter
	Moulding	Well ventilated area with minimum 5 micron filter
	Vulcanising	Normal air
	Packing	Air conditioned
Intra Uterine Devices	Moulding	Well ventilated area with minimum 5 micron filter
	Assembling	7
	Packaging	7
Tubal ring	Extrusion	7
	Cutting and Assembly	7
	Packaging	7
Blood bags	Moulding/Extrusion of components	8
	Assembly	7
	Filing	5
Suture	Extrusion	9
	Assembly	8
	Packing	8
Staplers	Staple formation	9
	Staple assembly	8

	Staple final pack	8

Ligatures	Extrusion	9
	Cutting and assembly	8
	Final Pack	8
Surgical dressings	Weaving	9
	Assembly and Gauzing	9
	Final pack	9
In-vitro diagnostics Kit/Reagents	Dry, Liquid Reagent Preparation	Well Lighted and Ventilated controlled temperature & humidity as per process or product requirement
	Coating of sheets etc.	
	Assembly and primary packing	
	Filling	Well Lighted and Ventilated controlled temperature and humidity as per process or product requirement. Provision of Laminar hood if required, Clean Room class 8 or class 9 as per product/process requirement
	Secondary Packing	Well Lighted and Ventilated controlled temperature if required
	Storage	As per recommended storage condition of the product].