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(SCHEDULE MIII)

GOOD MANUFACTURING PRACTICES AND REQUIREMENTS OF PREMISES, PLANT AND EQUIPMENT FOR MEDICAL DEVICES AND IN-VITRO DIAGNOSTIC KITS & REAGENTS

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CENTRAL DRUGS STANDARD CONTROL ORGANIZATION
DIRECTORATE GENERAL OF HEALTH SERVICES
MINISTRY OF HEALTH & FAMILY WELFARE
GOVT. OF INDIA,

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[SCHEDULE M III]

GOOD MANUFACTURING PRACTICES AND REQUIREMENTS OF PREMISES, PLANT AND EQUIPMENT FOR MEDICAL DEVICES AND IN VITRO DIAGNOSTIC KITS & REAGENTS

Note: To achieve the objectives listed below, each licensee shall evolve a quality system in line with BIS 15579/ISO 13485 as amended. In the case of combination devices, the process of manufacture of the drug/biologics will be as per schedule M. However the process of loading of drug/biologics on to the device and thereafter will be governed by this schedule. No part of the Schedule M shall be applicable for medical device and in-vitro diagnostic kits and reagents manufacture.

PART-A
(SPECIFIC REQUIREMNTS OF FACTORY PREMISES FOR MANUFACTURE OF NOTIFIED MEDICAL DEVICES)

A.1 GENERAL REQUIREMENTS:

A.1.1. Location and surroundings.- The factory building(s) for manufacture of devices 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.

A.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 medical devices under hygienic conditions. They shall conform to the conditions laid down in the Factories Act, 1948 (63 of 1948) as amended from time to time,

The premises used for manufacturing, assembling, packaging, labelling, warehousing shall be –

(i) adequately provided with working space to allow orderly and logical placement of equipment, materials and movement of personnel so as to avoid the possibilities of mix ups by providing suitable mechanism;

(ii) 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;

(iii) air-conditioning, where ever prescribed for the manufacturing operations. The manufacturing areas shall be well lighted, effectively ventilated, with air control facilities as required and may have proper Air Handling Units (wherever applicable) to maintain required conditions including temperature and, wherever necessary, humidity, as defined for the relevant product. These

conditions shall be appropriate to the category of device 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;

(iv) 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;

(v) the walls and floors of the areas where manufacture of devices 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 inspection of the premises shall be maintained.

(vi) the buildings shall be built on proper foundation with standardized materials to avoid cracks in critical areas assembling and primary packing area.

(vii) 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 the clean area.

(viii) the manufacturing areas shall be clearly separated into support areas (e.g. washing and component preparation areas, storage areas etc.), preparation areas (e.g. non-aseptic blending areas etc. in the case of combination devices.) 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.

(ix). the design, construction and validation of the clean room shall be done as per ISO 14644, or its equivalent developed by Bureau of Indian standards and revised from time to time, consists of the following parts, under the general title Cleanrooms and associated controlled environments :

- Part 1 : Classification of air cleanliness
- Part 2 : Specifications for testing and monitoring to prove continued compliance with ISO 14644-1
- Part 3 : Test methods
- Part 4 : Design, construction and start-up
- Part 5 : Operation
- Part 6 : Vocabulary
- Part 7 : Separative devices (clean air hoods, glove boxes, isolators and mini-environments)
- Part 8 : Classification of airborne molecular contamination

A.1.3 Disposal of waste. -

(i) the disposal of sewage and effluents (solid, liquid and gas) from the manufacture 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 devices. The same shall be disposed to the approved vendors as prescribed by the State and Central pollution control board acts 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.

A.2. Warehousing Area:

A.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, in process, and finished products, products in quarantine, released, rejected, returned or recalled, machine and equipment spare parts and change items.

A.2.2 Warehousing areas shall be designed and adapted to ensure good storage practices are maintained. 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.

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

A.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.

A.2.5. In case of combination device manufacture, there shall be a separate sampling area with enclosures in the warehousing area for drugs/biologics. However in the case of storage of plastic components, there is no need for a separate sampling enclosure. A designated area for sampling is sufficient.

A.2.6. Segregation/demarcation shall be provided for the storage of rejected, recalled or returned materials or products. Such areas, materials or products shall be suitably marked.

A.2.7. Adequate fire protection measures shall be provided in conformity with the rules of the concerned civic authority.

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

A.2.9. Storage of hormones in case of combination devices 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.

A.2.10. Wherever required, sampling of sterile components shall be conducted under aseptic conditions, which can also be performed in a dedicated area within the manufacturing facility.

A.2.11. Rodent treatments (Pest control) should be done regularly and at least once in a year and record maintained.

REQUIREMENTS FOR MEDICAL DEVICE MANUFACTURE

A.3. Manufacturing area:

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

A.3.2. In order to avoid the risk of cross-contamination in the case of devices with drugs/biologicals, separate dedicated and self- contained facilities shall be made available.

A.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.

A.3.4. Pipe-work, electrical fittings, ventilation openings and similar service lines shall be designed, fixed and constructed to avoid 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.

A.3.5 The manufacture of medical devices shall be broadly divided into the following separate operations/Sections:-

(1) Plastic processing (wherever manufacture of components is to start from granules).
(2) Foundry, plating, polishing, turning and shaping etc for metal implants
(3) Cleaning as applicable
(4) Component storage
(5) Assembling
(6) Final pack.
(7) Sterilization(wherever sterilization is in-house)
(8) Aeration if applicable
(9) Finished product storage

Note: the plastic processing area shall be class D clean room. The foundry, turning, polishing area shall operate with filtered air with AHU of suitable capacity. The cleaning area of the components which is assembled on to the product shall have the same classification of the area where it is assembled.

The Non sterile medical devices shall be manufactured and assembled in class D clean room so as to minimize the contamination on the products. Wherever possible the non-sterile devices shall be cleaned using ultrasonic cleaning process to remove the dust. All cleaning operations of components/products shall be carried out using demineralized water.

A.4. Ancillary Areas:

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

A.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.

A.4.3 Maintenance workshops shall be separate and away from manufacturing areas. Whenever spares, changed parts and tools are stored in the manufacturing 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.

A.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 manufacturing purposes.

A.5. Quality Control Area.

A.5.1. Quality **Control** Laboratories if available shall be independent of the production areas. Separate areas shall be provided each for physico-chemical, biological, microbiological or radio-isotope analysis. 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.

A.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, reagents and records.

A.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.

Note: If the manufacturer intend to do the physical/chemical/biological testing outside, the same shall be carried out in the external testing laboratory approved by the State/ Central Licensing authority without separate approval.

A.6. Personnel

A.6.1. The manufacture shall be conducted under the direct with personnel of competent technical staff with prescribed qualifications and practical experience I for medical device.

A.6.2 The head of the Quality Assurance 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.

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

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

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

A.6.6. There shall be a documented process in place through which all the Quality Assurance, Production, Maintenance personnel are trained and retrained at a predetermined interval, in the respective standard operating procedures and the records of the same shall be maintained in line with the requirements specified in BIS 15579.

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

A.7.1 The personnel handling antibiotics, hormones and other potent drugs in the case of combination devices 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.

A.7.2 All the employees shall undergo medical examination for communicable or contagious diseases. They shall also be subjected to annual medical examination and the records thereof shall be maintained.

A.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.

A.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 finished goods until his condition is no longer judged to be a risk.

A.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 and records of the same shall be maintained.

A.7.6 As far as possible, direct contact shall be avoided between the unprotected hands of personnel and raw materials, intermediate or finished, unpacked products.

A.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, 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.

A.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.

A.7.9 This section covers garments required for use by personnel working only in clean room area. Outdoor clothing shall not be brought into the clean room areas. In addition to the below the requirements of ISO 14644 also will be applicable.

A.7.10 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.

A.7.11 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.

A.7.12 Only clean, sterilized and protective garments shall be used at each work session where aseptic 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.

A.7.13 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.

A.7.14. The footwear shall be of suitable plastic or rubber material and shall be daily cleaned with a bactericide.

A.7.15 Safety goggles or numbered glasses with side extension shall be used inside aseptic areas. These shall be sanitized by a suitable method.

A.7.16 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.

A.8. Quality Management system

The manufacturer shall set up and maintain a quality management system in line with BIS 15579/ISO 13485 as amended

A.8.1 The quality management system appropriate to the manufacture of medical devices shall

ensure that: –

a. the medical devices are designed and developed in a way that takes account of the requirements of Essential Principles of safety and efficacy of Medical devices, 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. The clinical evaluations of the product shall be carried out as per ISO 14155 standards as amended or Equivalent Indian Standards as amended from time to time.

c. There shall be a validated quality plan for the entire operations and shall be documented.

A.9. Manufacturing Operations and Control:

A.9.1 All manufacturing operations shall be carried out under the supervision of technical staff approved by the Licensing Authority. Each critical step in the process product realization shall be performed by trained personnel under the direct personal supervision of approved technical staff.

The all the products in the manufacturing area shall be labelled with information like the name of the component, stage, batch no and quantity so that identification and traceability is maintained at all times during manufacture. Each label should be initialed and dated by the authorized technical staff..

A.9.2. Precautions against mix-up and cross-contamination:

A.9.2.1. The licensee shall prevent mix-up and cross-contamination of device components 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. In case of the manufacture of Non sterile devices, the manufacture shall be required to have filtered air supply in to the production area and the area shall be temperature controlled.

A.9.2.2 The licensee shall ensure processing of sensitive drugs (in the case of combination devices) in segregated areas or isolated production areas within the building with independent air-handling unit and proper pressure differentials. The effective segregation of these areas shall be validated with adequate records of maintenance and services.

A.9.2.3 To prevent mix-ups during manufacturing stages, material under process shall be conspicuously labelled to demonstrate their status. All equipment used for production shall be labelled with their current status.

A.9.2.4 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, components and packing materials. The line setup shall be performed according to an approximate check list and recorded. This shall be the part of the device history record.

A.9.2.5 Packaging lines shall be independent and adequately segregated. It shall be ensured that all left-overs of the previous packaging operations, including labels, are cleared by providing line clearance and the same shall be recorded.

A.9.2.6 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 checked at the beginning of the printing operation against the control print matter record and recorded. Sample of the print matter shall be either printed or pasted in the verification record. This shall be maintained at the printing area throughout the manufacture of the batch. This record with periodic inspections shall be the part of device history record.

A.9.2.7 The manufacturing environment shall be maintained at the required levels of temperature, humidity and cleanliness and shall be routinely validated. The records of temperature and the bio burden shall be reviewed and maintained for clean areas.

A.9.2.8 Authorised persons shall ensure change-over into specific uniforms before undertaking any manufacturing operations including packaging.

A.9.2.9 There shall be segregated secured areas for recalled or rejected material and for such material which are to be reprocessed or recovered.

A.9.3. Sterile Devices:

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

A.9.3.1 Validation is an integral part of the Good manufacturing practices for medical devices. The manufacturing process shall be routinely validated as per the validation master plan and output of such process shall not be tested for each and every parameter. With respect to Sterilization Operation, which undergo validation at a predefined interval, the batch/ lot shall be released based on parametric release of the process and not based on Sterility testing. In the case of sterilization by ETO, if the process is validated as per ISO 11135 standards or equivalent standards of Bureau of Indian standard, then residual ETO testing need not be carried out for each batch**.**

A.9.3.2. The manufacturing process like milling etc. should be housed in such a way that the operations do not contaminate the processing area. Such operations should be conducted outside clean room and the output of the operation should undergo ultrasonic cleaning to remove dust particles.

A.9.3.3**Terminally sterilized products.–**

A.9.3.4.1. Where there is a risk to the product/ components from microbial contamination, the above operation shall be done in Grade C environment. All the processes shall be validated..

A.9.3.4.2. Manufacture of all products requiring terminal sterilization shall be done under Grade C clean room.

A.9.3.4.3 The assembling and packaging of sterile components which will not be further sterilised, shall be carried out in a Grade A environment with Grade B in background.

A.9.3.4.4. Sterilization (Autoclaving).–

A.9.3.4.4.1. Before any sterilization process is adopted, the process shall be validated as per ISO 17655

A.9.3.4.4.2. 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.

A.9.3.4.4.3. The sterilizer shall be double ended to prevent mix-ups.

A.9.3.4.4.4. Periodic bio-burden monitoring of products (pre sterility counts) before terminal sterilization shall be carried out and controlled to limits specified for the product.

A.9.3.4.4.5. 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.

A.9.3.4.4.6. 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. The batch shall be released based on the parametric release as long as the product is validated

A.9.3.4.4.7. Wherever the sterilization process is being validated and has a revalidation schedule, the parametric release shall be adopted for the release of output of the process. In such cases, the routine sterility testing shall not be mandated.

A.9.3.4.4.8 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.

A.9.3.4.5 Sterilization (By dry heat).–

A.9.3.4.5.1. The sterilization process shall be carried out as per ISO 20857 or equivalent standards developed by Bureau of Indian Standards and revised from time to time.

A.9.3.4.5.2. Chemical or biological indicators may also be used, but shall not take the place of physical validation.

A.9.3.4.6 Sterilization (By Moist Heat).-

A.9.3.4.6.1 The sterilization process as well as validation and revalidation shall be carried out as per ISO 17665 or equivalent standards developed by Bureau of Indian standards

A.9.3.4.6..2 The products to be sterilized, other than products in sealed containers, shall be packed 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 and pressure for the required time.

A.9.3.4.7 Sterilisation by ETO

A.9.3.4.7.1 The sterilization process by ETO shall be validated and revalidated as per ISO 11135 or equivalent standards of Bureau of Indian Standards as developed from time to time.

A.9.3.4.7.2. The presterility microbial count is an important parameter which need to be controlled on the product and the same shall be carried out as per ISO 11737 or equivalent Indian standards developed from time to time.

A.9.3.4.8 Sterilisation by Gamma radiation

A.9.3.4.8.1 The Gamma radiation sterilization process shall be validated and revalidated as per ISO 11137 or equivalent standards of Bureau of Indian Standards as developed from time to time.

A.9.3.4.8.2 The presterility microbial count is an important parameter which need to be controlled on the product and the same shall be carried out as per ISO 11737 or equivalent Indian standards developed from time to time

A.9.3.4.8.3 Where ever possible, the products shall be irradiated with a minimum dosage of 2.5 Mrad. However, only if the polymer used will degrade at 2.5 Mrad , then lower dosage shall be used based on the validation data.

A.9.3.4.9. Completion/finalisation of sterile products–

A.9.3.4.9.1. All unit operations and processes in the manufacture of a batch shall be as per the validated parameters. .

A.9.3.4.9.2. The packages shall be validated and revalidated suitability to ensure that the integrity of the package is maintained throughout the shelf life.

A.9.3.4.9.3. Routine testing is not required on parameters which are being validated and will be revalidated, on the product.

A.10. Sanitation in the Manufacturing Premises:

A.10.1 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 validated cleaning procedure shall be maintained.

A.10.2 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.

A.10.3 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
c. personnel assigned to and responsible for the cleaning operation.

A.10.4 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 medical devices 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.

A.10.5 Production areas shall be well lit, particularly where visual on-line controls are carried out.

A.10.6 There shall be written procedures for the sanitation of clean room processing facilities. Employees carrying out sanitation of aseptic areas shall be trained specifically for this purpose.

A.10.7 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.

A.10.8. 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.

A.10.9. 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.

A.10.10 Cleaning of sterile processing facilities shall be undertaken with air suction devices or with non-linting sponges or clothes.

A.11. Raw Materials and Components:

A.11.1 The licensee shall keep an inventory of all raw materials and components to be used at any stage of manufacture of the device and shall maintain records.

A.11.2 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.

A.11.3 All incoming materials shall be purchased from approved vendors. There shall be an approved supplier list. There shall be a system of approving a supplier and validating vendors.

A.11.4 Authorized staff appointed by the licensee in this behalf, which may include personnel from the Quality Assurance Department, shall undertake the receiving inspection. There shall be approved SOP /Work instruction for the receiving inspection.

A.11.5 Statistical sampling tools shall be used for sampling of the receipts. The sampling of components shall be conducted as per single normal plan general inspection level II as prescribed in ISO 2589. The Acceptance Quality Level (AQL) shall be predetermined based on the criticality of the test conducted. As a general rule for critical defects AQL shall be between 0 to 0.65,Major A defect shall be between 1.0 and 1.5, Major B defect shall be between 1.5 to 2.5 and minor defect shall be 4 and above.

A.11.6 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
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 (if applicable).

A.11.7 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.

A.11.8 Cartons from which samples have been drawn shall be identified.

A.11.9 Only raw materials and components which have been released by the Quality Assurance Department shall be used. In case of combination products, for pharmaceutical ingredients used, it shall be ensured that shelf life of formulation product shall not exceed with that of active raw materials used. However in the case of polymer, metal components, this is not applicable.

A.11.10 It shall be ensured that all the containers of raw materials and components are placed on the raised platforms/racks and not placed directly on the floor.

A.12. Equipment:

A.12.1 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 minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt and, in general, any adverse effect on the quality of products. Each equipment shall be provided with a logbook, wherever necessary.

A.12.2 Weighing 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.

A.12.3 In the case of combination devices, the parts of the production equipment that come into contact with the product having Pharmaceuticals shall not be reactive, additive or adsorptive to an extent that would affect the quality of the product. This is not applicable for equipment's processing polymer components. However it shall be ensured that the equipment parts coming in to contact with polymers, metals etc. of the components/products shall be clean.

A.12.4 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.

A.12.5 Defective equipment shall be removed from production and Quality assurance areas or appropriately labelled.

A.12.6 All equipments installed shall have installation qualification and Operation qualification records.

A.12.7 The special equipment required for manufacturing sterile products

A.12.7.1. Unit-sterilizers shall be double-ended with suitable inter-locking arrangements between the doors. The effectiveness of the sterilization process shall be established validated as per ISO 17665, 11135, 11137 respectively for steam, ETO and Gamma sterilization respectively. Various sterilization parameters shall be established based on these studies and documented.

A.12.8 On procurement of equipment, there shall be an established documented process for Installation qualification, Operational qualification and process qualification of each of the equipment /operation and shall be validated.

A.12.9. Standard Operating Procedures/Work Instructions 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.

A.13. 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 device for sale and to provide an audit trail that shall permit investigation of the history of any suspected defective batch. The manufacturers shall comply with the requirements of document control as per BIS 15579.

A.13.1 Documents designed, prepared, reviewed and controlled, wherever applicable, shall

comply with these rules.

A.13.2 Documents shall be approved, signed and dated by appropriate and authorized persons. The review of the production records shall be carried out by Quality Assurance personnel.

A.13.3 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 dated. There shall be no overwriting in the manufacturing/quality assurance documents.

A.13.4 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 devices 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. In case of non sterile devices, the records shall be kept for a period of 25 years from the date of manufacture.

A.13.5 Data may be recorded by electronic data processing systems or other reliable means, in such conditions, the same shall be compliant to data security. Record of security validation shall be maintained. This shall be validated at predetermined intervals 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.

A.13.6 All operating systems of the machines, independent softwares used in either manufacture or quality assurance shall be compliant to ISO 62304 or any equivalent Indian standards which are developed from time to time.

A.13.7 The device history records relating to manufacture of sterile products shall include:-

- Manufacturing/processing records of plastic processing (if applicable)
- Drug processing record(in case of combination product)
- Staging record for the components and packing materials
- In process verification records, test record
- In process production record of each stage of manufacture
- Production reconciliation and Investigation record if applicable
- Label reconciliation record
- Sterilisation record
- Parametric monitoring record
- Records of plate-counts of environmental bio burden whenever applicable.
- Pre sterility bio burden count on the product wherever applicable
- Final yield summary sheet and investigation if any
- Numbers of components rejected at each stage
- Theoretical yield, permissible yield, actual yield and variation thereof.
- Investigation on variation in yield beyond permissible yield.
- Reference numbers of relevant analytical reports if applicable
- Finished product testing record summary and all attachments related to it
- Details of rework, if any.
- Reference of all operators carrying out different activities.
- Specimens of printed packaging materials.
- Records of destruction of rejected components and printed packaging materials.

- Signature of the reviewing competent technical staff responsible for Quality Assurance.

Note:

i. Products shall be released only after complete review of the batch/ lot record.
ii. The parametric release data relating to sterilisation shall be maintained.
iii. Validation records shall be maintained separately,
iv. Records of environmental monitoring like temperature, humidity, microbiological data, etc. shall be maintained.
v. Records of periodic servicing of HEPA filters, sterilizers and other periodic maintenance of facilities and equipment carried out also be maintained separately.

A.14. Labels and other Printed Materials

Labels are absolutely necessary for identification of the devices 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.

A.14.1 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).

A.14.2 To avoid chance mix-up of printed packaging materials, product leaflets, relating to different products, shall be stored separately.

A.14.3 Prior to release, all labels for containers, cartons and boxes and all circulars, inserts and leaflets shall be examined by the Quality Assurance Department of the licensee.

A.14.4 Prior to packaging and labelling of a given batch of a device, it shall be ensured by the licensee that samples are drawn from the bulk and duly tested, approved and released by the quality assurance personnel.

A.14.5 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.

A.15. Internal audit/Quality audit

It may be useful to constitute an audit team supplemented with a quality audit procedure for assessment of all or part of a system with the specific purpose of improving it. The requirements of the internal audits as mentioned in BIS 15579 shall be complied with.

A.15.1 To evaluate the manufacturer's compliance with GMP/quality system in all aspects of manufacturing, concept of internal audit shall be followed. The manufacturer shall constitute a team of independent, experienced, qualified persons from within or outside the company, who is trained in auditing as well as have sound knowledge of device manufacturing and who can audit objectively the implementation of methodology and procedures evolved. The procedure for internal

audit shall be documented indicating audit results, evaluation, conclusions and recommended corrective actions with effective follow up program. The recommendations for corrective action shall be adopted.

A.15.2 The program shall be designed to detect shortcomings in the implementation of Quality system/ Good Manufacturing Practice and to recommend the necessary corrective actions. Internal audits 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 internal audit shall consist of personnel who can evaluate the implementation of Good Manufacturing Practice objectively; all recommendations for corrective action shall be implemented.

A.15.3 Written instructions for internal audit shall be drawn up.

16. Quality Control

Quality Control shall be concerned with sampling, specifications, Raw material/in process /finished product 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. The department as a whole shall have other duties such as to establish, evaluate, validate and implement all Quality Assurance Procedures and methods.

A.16.1 The Licensee shall either have his own testing facilities with qualified staff or shall use contract test laboratories approved by the State or Central Licensing Authority.

A.16.2 In case the manufacturer decides to have his own laboratory, the area of the quality Assurance laboratory may be divided into Chemical, Instrumentation, Microbiological and Biological testing and shall be manned with personnel with appropriate qualification.

A.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.

A.16.4 Standard operating procedures / Work instructions 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.

A.16.5 There shall be authorized and dated. Specifications for all materials, and components and an approved supplier list.

A.16.6 No batch of the product shall be released for sale or supply until it has been reviewed by the Quality Assurance Manager that the batch has been manufactured in accordance with the quality plan requirements of the standards laid down.

A.16.7 Wherever possible, reference/retained samples from each batch of the products

manufactured shall be maintained in quantity which is sufficient for the devices required to conduct all the functional tests. In case of retaining the samples of the products is not possible, then the reference raw materials/components used shall be retained to a minimum of 20 years.

A.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 quality assurance before a product is released for sale or distribution.

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

A.16.10 The quality assurance department shall conduct accelerated/ real time 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.

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

A.16.12 All instruments shall be calibrated and testing procedures validated before these are adopted for routine testing. Periodical calibration of instrument and validation of procedures shall be carried out. A revalidation calendar is maintained by the Quality Assurance.

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

A.16.14 Reference standards, working standards, and other reference materials and technical books, as required, shall be available in the Quality Assurance Laboratory of the licensee.

A.16.15. The licencee shall ensure that the product manufactured comply with the requirement of ISO 10993 standards or its equivalent Indian standards

A.16.16 The licencee shall carry implement a risk management process in line with ISO 14971 standards or its equivalent Indian standards and the same shall be revalidated periodically based on the performance of the product in the market

A.16.17 The products /components with materials derived from animal/human orgin, biological evaluation need to be carried out. Wherever applicable TSC/BSC evaluation need to be done.

A.16.18. There shall be a documented post market vigilance program and the same shall be implemented and reports thereof shall be maintained.

A.17. Specification

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

- the designated name and internal code reference;
- reference, if any, to a pharmacopoeia monograph if applicable(in case of combination products)
- qualitative and quantitative requirements with acceptance limits;
- name and address of manufacturer or supplier and original manufacturer of the material;
- specimen of printed material;
- directions for sampling and testing or reference to procedures;
- storage conditions; and
- maximum period of storage before re-testing.

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A.17.2. For in-process. - Specifications for in-process material, intermediate and bulk products shall be available. The specifications should be authenticated.

A.17.3 For finished products. - Appropriate specifications for finished products shall include:

- the designated name of the product and the code reference
- directions for sampling and testing or a reference to procedures wherever applicable;
- a description of the device and package details;
- the qualitative and quantitative requirements, with the acceptance limits for release;
- the storage conditions and precautions, where applicable, and
- the shelf-life.

A.17.4 All softwares used in the device/equipment for testing and manufactures shall be validated.

A.18. Technical File (Master Device Record):

There shall be Master Device records (MDR) 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 MDR shall include:

a. the name of the product together with product reference code relating to its specifications, drawings, photographs;
b. the name of the product along with the family name, a description of the device as well as the standard batch size if applicable;
c. Essential principle checklist
d. Risk management document(shall be updated periodically based on the performance data of the device) as per ISO 14971
e. Bio compatibility data as per ISO 10993
f. In case of devices with animal/human orgin, biological safety data
g. Product verification and validation data

h. In case of Sterile devices, sterilization validation data
i. Clinical evaluation data including the current reports on the performance of the devices. The clinical evaluations shall be carried out as per ISO 14155 or equivalent BIS specification as may be developed from time to time.
j. Name, quantity, and reference number of all the starting materials to be used.
k. In the case of the assembling operations, a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.
l. a statement of the processing location and the principal equipment to be used.
m. the methods, or reference to the methods, to be used for preparing the critical equipment including cleaning, assembling, calibrating, sterilizing;
n. detailed stepwise processing instructions for each step; List of SOPs/ Validated processes and their revalidation schedule
o. the instructions for in-process control with their AQLs;
p. the requirements for storage conditions of the products, including the container, labelling and special storage conditions where applicable;
q. any special precautions to be observed;
r. packing details and specimen labels including IFUs,.

A.19. Packing Records:

There shall be approved 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) the packaging configuration and packaging validation data
(c) 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.;
(d) reproduction of the relevant printed packaging materials and specimens indicating where batch number and expiry date of the product have been applied;
(e) 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.
(f) description of the packaging operation, including any significant subsidiary operations and equipment to be used;
(g) details of in-process controls with instructions for sampling and acceptance; and
(h) 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.

A.20. Device History Records (DHR):

A.20.1 A DHR shall be kept for each batch or part batch assembled and produced. It shall be based on the relevant parts of

a. the packaging instructions, and the method of preparation of such records shall be designed to avoid transcription errors.

b. Before any assembly/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 through a line setup and line clearance record.

c. 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.

d . During processing, the following information shall be recorded at the time each action is taken and the record shall be dated and signed by the person responsible for the processing operations and reviewed by QA and the DHR shall have at a minimum the following records : -

- Manufacturing/processing records of plastic processing (if applicable)
- Drug processing record (in case of combination product)
- Staging record for the components and packing materials
- In process verification records, test record
- In process production record of each stage of manufacture
- Production reconciliation and Investigation record if applicable
- Label reconciliation record
- Sterilisation record
- Parametric monitoring record
- Records of plate-counts of environmental bio burden whenever applicable.
- Pre sterility bio burden count on the product wherever applicable
- Final yield summary sheet and investigation if any
- Numbers of components rejected at each stage
- Theoretical yield, permissible yield, actual yield and variation thereof.
- Investigation on variation in yield beyond permissible yield.
- Reference numbers of relevant analytical reports if applicable
- Finished product testing record summary and all attachments related to it
- Details of rework, if any.
- Reference of all operators carrying out different activities.
- Specimens of printed packaging materials.
- Records of destruction of rejected components and printed packaging materials.
- Signature of the reviewing competent technical staff responsible for Quality Assurance

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

A.22.1 Receipt of materials:

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

A.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.

A.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.

A.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.

A.22.2 Sampling:

There shall be written Standard Operating Procedures for sampling which include the person(s) authorized to take the samples. Unless otherwise validated IS 2500 standards for statistical sampling shall be used.

A.22.3. Batch/ Lot Numbering

A.22.3.1There shall be Standard Operating Procedures describing the details of the batch (lot) numbering set up with the objective of ensuring that each batch of components, finished devices are identified with a specific batch number.

A.22.3.2 Batch numbering Standard Operating Procedures applied to a processing stage in the manufacture of the components of the medical device. More than one batch of components shall be used for assembling a batch of the product provided that the components shall be identified using a separate identity in the batch number as sub batches so that they are traceable

A.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.

A.22.3.4. Batch numbering shall be done in such a way that the date of manufacture of the product could be identified from the batch number configuration. In such a case the date of manufacture shall not be printed on to the package.

A.22.4.Testing:

If the testing is carried out in house, 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.

A.22.5 Records of analysis:

A.22.5.1 If testing is carried out in-house, the records shall include the following data:

(a) name of the material or product
(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.

A.23. Reference Samples:-

A.23.1 Each lot of raw materials/ components received, in a quantity sufficient to carry out all the functional testing, shall be retained for a period of 20 years of the last batch produced from that raw material/ component.

A.23.2. Samples of finished devices shall be stored to carry out all the tests of functionality. In lieu of this, components/ raw materials received shall be stored as reference samples.

A.24. Reprocessing and Recoveries:

A.24.1.Where rework is necessary, written procedures shall be established, validated and approved by the Quality Assurance Department.

A.24.2.If the product batch has to be reworked, 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. Process FMEA should be performed to understand the risks and the corrective actions in place to mitigate the risk shall be recorded. Based on the risk evaluation, the re-processed batch shall be subjected to stability evaluation.

A.24.3.All implantable polymer based components shall be formed using virgin materials. Reprocessing of polymers during polymer processing is prohibited. However if the polymer is used for manufacture of components which do not come in to contact with the body fluids or do not transport fluids in to the body then reprocessing shall be done provided the reprocessing donot affect the mechanical properties of the product.

A.25. Distribution records:

A.25.1.Prior to distribution or dispatch of given batch of a device, it shall be ensured that the device history record has been reviewed, approved and released by the Quality assurance personnel. Pre-dispatch visual inspection shall be performed on each consignment on a random basis to ensure that only the correct goods are dispatched. Periodic audits of warehousing practices followed at distribution centers shall be carried out and records thereof shall be maintained. Standard Operating Procedures as per the Good distribution Practice Guidelines shall be developed for warehousing of products.

A.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.

A.26. Validation and process validation:

A.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, Sterilization, sterility testing, residual ETO testing, clean room working conditions etc.

A.26.2.A written report summarizing recorded results and conclusions shall be prepared, documented and maintained. This shall be reviewed at a predetermined interval as shall be established.

A.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 validated prospectively or retrospectively.

A.26.4.When any new process 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 consistent output of the required quality.

A.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 validated..

A.27. Product Recalls:

A.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 as per the rapid alert guidelines. The licensee may make use of both print and electronic media in this regard.

A.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.

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

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

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

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

A.27.7. The licencee shall have a mock recall in place to demonstrate the ability of the quality system to take back the defective devices at a shortest possible time.

A.28. Complaints and Adverse Reactions:

A.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. The complaints shall be recorded, maintained, tracked in an electronic software which has been validated.

A.28.2. Reports of serious adverse reactions resulting from the use of a device along with comments

and documents shall be forthwith reported to the concerned licensing authority. The serious adverse events shall be such events as described in the SAE reporting form reflected in the Pharmacovigilance site of the CDSCO.

A.28.3 There shall be written procedures describing the action to be taken, recall to be made of the defective product. This shall also include the requirement of Risk analysis in case of an adverse event.

A.29. Site Master File

The licensee shall prepare a succinct document in the form of 'Site Master File' containing the details of the quality systems in place, details of manufacture, quality plan, manpower, qualifications of key personnel etc. on the operations carried out at the licensed premises. It shall contain the following: -

A.29.1 General information:

- brief information of the firm;
- List of Board of Directors
- device manufacturing activities as permitted by the licensing authority;
- other manufacturing activities, if any, carried out on the premises;
- type of products licensed for manufacture with flow charts mentioning procedure and process flow; list of outsourced activities
- number of employees engaged in the production, quality assurance, storage and distribution;
- use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;
- short description of the Quality Management System of the firm; and
- products details registered with foreign countries.

A.29.2 Personnel:

- organisational chart showing the arrangement for quality assurance including production and quality assurance;
- qualification, experience and responsibilities of key personnel;
- health requirements for personnel engaged in production; and
- personnel hygiene requirements, including clothing.

A.29.3 Premises:

- simple plan or description of manufacturing areas drawn to scale;
- nature of construction and fixtures/fittings;
- 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;
- special areas for the handling of the highly toxic, hazardous and sensitizing materials;
- description of planned preventive maintenance programs for premises and of the recording

system.

A.29.4 Equipment:

- brief description of major equipment used in Production and Quality Assurance Laboratories (a list of equipment required);
- description of planned preventive maintenance programs for equipment and of the recording system; and
- qualification and calibration including the recording systems and arrangements for software validation.

A.29.7 Production:

- brief description of production operations using, wherever possible, flow chart
- handling of non-conforming products;
- brief description of general policy for process validation.

A.29.8 Loan licence manufacture and licensee:

- The licensee shall subcontract a part of the manufacturing activity
- description of the way in which compliance of Good Manufacturing Practices by the loan licensee shall be assessed.

A.29.9 Distribution, complaints and product recall:

- arrangements and recording system for storage and distribution;
- arrangements for the handling of complaints and product recalls.

A.29.10 Internal audit

A short description of the internal audit indicating whether an outside, independent and experienced external expert was involved in evaluating the manufacturer's compliance with quality Management systems in all aspects of production.

A.29.11 Export of devices

- products exported to different countries;
- complaints and product recall, if any
- Regulatory actions by regulatory authorities in the exporting country.

PART-B
(SPECIFIC REQUIREMNTS OF FACTORY PREMISES FOR MANUFACTURE OF IN-VITRO DIAGNOSTICS KITS & REAGENTS)

B.1 GENERAL REQUIREMENTS

B.1.1 Location and surroundings

The factory building(s) for manufacture of in- vitro diagnostic reagents/kits shall be located, preferably in an industrial area and 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 produces disagreeable or obnoxious, odour, fumes, excessive soot, dust, smoke, chemical or biological emissions.

B.1. 2 Buildings and premises

The building(s) used for the factory shall be such as designed, constructed, adapted and maintained to suit the manufacturing operations so as to permit production of in vitro diagnostic reagents / kits under hygienic conditions. They shall conform to the conditions laid down in the factories Act, 1948 (63 of 1948) as amended an,

The premises used for manufacturing, processing, warehousing, packaging, labeling and testing purposes shall be -

(i) Compatible with other diagnostics 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 to:

(a) Avoid risk of mix-up between different items of diagnostic reagents 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, vermin, and rodents. Interior surface (walls, floors, and ceilings) shall be smooth and free from cracks, and permit easy cleaning, painting and disinfection;

(iv) Air-conditioning, where ever prescribed for the operations and manufacture of in-vitro diagnostic kits/ reagents under production. The production and dispensing areas shall be well lighted & effectively ventilated. Wherever necessary, it should have provision for controlled temperature & humidity as per the manufacturing process. These shall also be suitable to the comforts of the personnel working with protective clothing, products handled, and operations undertaken within them in relation to the external environment. These areas shall be regularly monitored to ensure compliance with required specifications;

(v) Provided with drainage system, preferably underground, which shall be of adequate size and so designed as to prevent back- flow and / or to prevent insects / rodents entering the premises. Open channels shall be avoided in manufacturing areas, but if inevitable these shall be shallow to facilitate cleaning and disinfection;

B.1. 3 Water system

There shall be a validated 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 to produce DEMINERALISED WATER of IP grade for manufacture of in-vitro diagnostic reagents / kits.

B.1. 4 Disposal of waste

(i)The disposal of sewage and effluents (solid, liquid and gas) from the factory 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) Rules1996.

(iii)Provision 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 Legislation.

B.1. 5 WAREHOUSING AREA

B.1. 5.1 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's parts/spare items.

B.1. 5.2 Warehousing areas shall be designed or adapted to ensure good storage-conditions. They shall be clean, dry and maintained within acceptable temperature limits. Where cold storage and other special storage conditions are required (e.g. temperature, humidity), these shall be provided,

monitored and recorded. Storage areas including cold storage shall have appropriate house – keeping and rodent, pests and vermin control procedures and records maintained.

B.1. 5.3 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 status. Access to these areas shall be restricted to authorized persons.

B.1. 5.4)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 / or materials shall be restricted.

B.1. 5.5 Materials 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 rules of the civic authority concerned

B.1. 5.6 Printed packaging materials shall be stored in safe separate and secure areas.

B.1. 5.7 Regular checks shall be made to ensure steps against spillage, breakage and leakage of containers.

B.1. 5.8 Rodent treatments (pest control) should be done regularly and at least once in a year and record maintained.

B.1. 6 Production area

B.1. 6.1 The production area shall be designed to allow the production in uni – flow and with logical sequence.

B.1. 6.2 Working and in-process warehousing space shall be adequate to permit orderly and logical positioning of equipment and materials and movement of personnel so as to avoid cross – contamination and to minimize the risk of omission or wrong application of any of the manufacturing and control measures.

B.1. 6.3 Pipe – work, electrical fittings, ventilation openings and similar service lines shall be designed, fixed and constructed to avoid creation of recesses. Service lines shall preferably be identified by colours and flow – direction shall be marked.

B.1. 7 Ancillary areas

B.1. 7.1 Rest and refreshment rooms shall be separate from other areas. These areas shall not lead directly to the manufacturing and storage areas.

B.1. 7.2 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 for such areas.

B.1. 7.3 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.

B.1. 7.4 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.

B.1. 8 Quality Control area

B.1. 8.1 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.

8.2 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 provide for biological, microbiological and radioisotopes, (if provided) testing areas. The laboratory shall be provided with regular supply of water of appropriate quality for cleaning and testing purposes.

B.1. 9 Personnel

B.1. 9.1 The manufacture shall be conducted under the active direction and personal supervision of competent technical staff with prescribed qualifications and practical experience in production of diagnostic reagents / kits.

B.1. 9.2 The head of the Quality Control Laboratory shall be independent of the manufacturing. The testing shall be conducted under the active direction and personal supervision of competent technical staff who shall be whole time employees of the licensee.

B.1. 9.3 Personnel for Quality Assurance and Quality Control operations shall be suitably qualified and experienced.

B.1. 9.4 Written duties of technical and Quality Control personnel shall be laid and followed strictly

B.1. 9.5 Each technical person shall be suitably trained to perform the assigned responsibilities. They shall be subjected to regular in-service training.

B.1. 9.6 Number of personnel employed shall be adequate and in direct proportion to the workload.

B.1. 9.7 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.

B.1. 10 Health, clothing and sanitation of workers

1 B.1. 0.1 All personnel prior to employment, shall undergo medical examinations including eye examination and shall be free from Tuberculosis, skin and other communicable and contagious diseases. Thereafter, they should be medically examined periodically, at least once in a year. Records shall be maintained thereof. All persons handling positive controls such as those for Hepatitis B shall be protected by suitable measures from hazards of such handling. The licensee shall provide the services of a qualified physician for assessing the health status of personnel involved in different activities.

B.1. 10.2All persons, prior to and during employment, shall be trained in the practices of 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.

B.1. 10.3 No person showing at any time an 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.

B.1. 10.4 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.

B.1. 10.5 Direct contact shall be avoided between the unprotected hands of personnel and starting materials, intermediate or finished unpacked products.

B.1. 10.6 All personnel shall wear clean uniform appropriate to their duties. Before entry to manufacturing areas, there shall be change rooms separate for each sex with adequate facilities for personal cleanliness such as wash basin with running water, disposable towels, hand dryers, soaps, disinfectants etc. The change rooms shall be provided with cabinets for the storage of personal belongings of the personnel.

B.1. 10.8 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.

B.1. 11 Manufacturing Operations and Controls

B.1. 11.1 All manufacturing operations shall be carried out under the supervision of competent 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.

B.1. 11.2 The contents of all vessels and containers used in the manufacture and storage during various manufacturing stages shall be conspicuously labeled with the name of the product, batch no., batch size and stage of manufacture. Each label should be initialed and dated by the approved technical staff.

B.1. 11. 3 Precautions against mix – up and cross – contamination

(a)The licensee shall prevent mix – up and cross – contamination of material and product by proper segregation, status labeling and cleaning procedures. Proper records and Standard Operating Procedures thereof shall be maintained.

(b)The licensee shall ensure processing of critical items in segregated areas or isolated production areas within the building. The effective segregation of these areas shall be demonstrated with adequate records of maintenance and services. In exceptional cases the principal of campaign production in the same facilities may be accepted provided that specific precautions are taken.

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

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

(e)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 contamination. The line clearance shall be performed according to an appropriate checklist and recorded.

(f)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
re – checked at regular intervals. All printing and over – printing shall be authorized in writing.

(g)The manufacturing environment shall be maintained at the degree required of temperature, humidity and cleanliness.

(h)Authorized persons shall ensure change – over into specific uniforms before undertaking any manufacturing operations including packaging.

(I)There shall segregated enclosed areas, secured for recalled or rejected material and for such material, which are to be re - processed or recovered.

B.1. 12 Sanitation in the manufacturing premises

B.1. 12.1 Dedicated and self – contained facilities shall be provided for the production of particular diagnostic preparation

B.1. 12.2 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 validated cleaning protocol shall be maintained.

B.1. 12.3 The manufacturing areas shall not be used for storage of materials, except for material being processed. It shall not be used as a general thoroughfare.

B.1. 12.4 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 cleaning operation.

B.1. 12.5 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 confusion between different pharmaceutical products or their components to avoid cross – contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

B.1. 12.6)Productions areas shall be well lit, particularly where visual on – line controls are carried out.

B.1. 12.7 Records of compliance in respect of sanitation shall be maintained for inspection.

B.1. 13 Raw materials

B.1. 13.1 The licensee shall keep an inventory of all raw–materials to be used at any stage of manufacture of diagnostics and maintain records as per Schedule - U.

B.1. 13.2 All incoming materials and finished products shall be quarantined immediately after receipt or processing. All materials and products shall be stored under appropriate conditions and in an orderly fashion to permit batch segregation and stock rotation by a “first-in: first-out´ principle. All incoming materials shall be checked to ensure that the consignment corresponds to the order placed.

B.1. 13.3 Starting materials shall be purchased from authentic sources under valid purchase vouchers. Whenever possible, raw materials should be purchased directly from the producers and suppliers.

B.1. 13.4 Authorized staff appointed by licensee in this behalf, which may include personnel form the quality control department, shall examine each consignment on receipt and shall check each container for integrity of package and seal. Damaged and underweight containers shall be identified, recorded and segregated.

B.1. 13.5 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.

B.1. 13.6 Raw materials in the storage area shall be appropriately labeled. 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 or rejected)

(d) The manufacturing date, expiry date and re – test date.

B.1. 13.7 There shall be adequate separate partitioned 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.

B.1. 13.8 Containers from which samples have been drawn shall be identified.

B.1. 13.9 Only materials which have been released by the Quality Control Department and which are with in their shelf life are used. In lieu of testing by the manufacturer, a certificate of analysis may be accepted from the validated supplier, provided the manufacturer establishes the reliability of the supplier's analysis through appropriate validation of the supplier's test results.

B.1. 13.10 It shall be ensured that all the containers of raw materials are placed on the raised platforms or in steel racks.

B.1. 14 Equipment

B.1. 14.1 Equipment shall be located, designed, constructed adapted, and maintained to suit the operations to be carried out. The layout and design of the equipment aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross–contamination, build–up of dust or dirt, and, in general any adverse effect on the quality of products. Each of the equipment shall be provided with a logbook wherever necessary.

B.1. 14.2 Balances and other measuring equipment of an appropriate range, accuracy and precision may 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.

B.1. 14.3 The parts of the production equipment that come into contact with the product shall not be reactive, additive or adsorptive to an extent that will affect the quality of the product.

B.1. 14.4 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.

B.1. 14.5 Defective equipment shall be removed from production and Quality Control areas or appropriately labeled.

B.1. 15 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.

B.1. 15.1 Documents designed, prepared, reviewed and controlled, wherever applicable, shall comply with these rules.

B.1. 15.2 Documents shall be approved, signed and dated by appropriate and authorized persons.

B.1. 15.3 Documents shall specify the title, nature and purpose. They shall be laid out to 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 dated.

B.1. 15.4 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 diagnostic 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.

B.1. 15.5 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 be available in a hard copy and the accuracy of the records shall be checked. 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.

B.1. 16 Labels and other Printed Materials

Labels are necessary for identification of diagnostic substances and their use. The printing of labels should be clearly legible. The label shall carry all the prescribed details about the product.

B.1. 16.1 All containers and equipment shall bear appropriate labels. Different color coded labels shall be used to indicate the status of a product (for example: under test, approved, passed, rejected).

B.1. 16.2 To avoid chance mix – up of printed and packaging materials, product leaflets, relating to different products, should be store separately.

B.1. 16.3 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.

B.1. 16.4Prior to packaging and labeling 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.

B.1. 16.5Records of receipt of all labeling 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.

B.1. 16.6 The label or accompanying document of reference standards and reference culture shall indicate concentration, date of manufacture, expiry date, where appropriate, date on which container was first opened and storage conditions, where appropriate.

B.1. 17 Quality Assurance

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

The system of quality assurance appropriate to the manufacture of diagnostic preparations shall ensure that:

(a) The diagnostic preparations 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).

(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 diagnostic preparations are not released for sale or supplied before authorized person 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 diagnostic preparations;

B.1. 18 Self inspection and Quality audit

It may be useful to constitute the 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.

B.1. 18.1 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 implementations of methodology and procedures evolved. The procedure for self–inspection shall be documented indicating self–inspection results, evaluation and conclusions and recommended corrective actions with effective follow up program. The recommendations for corrective action shall be adopted.

B.1. 18.2 The program shall be designed to detect shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self–inspections shall be performed routinely and on specific occasions, like product recalls or repeated rejections 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 GMP objectively; all recommendations for corrective action shall be implemented.

B.1. 18.3 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 programs
(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.

B.1. 19 Quality Control System

Quality control shall be concerned with sampling, specifications, testing, documentation, release procedures which ensured that the necessary and relevant tests are actually carried and that the materials are not released for use, nor products were 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.

B.1. 19.1 Every manufacturing establishment shall establish its own Quality Control laboratory manned by qualified and experienced staff.

B.1. 19.2 Adequate area having the required storage conditions shall be provided for keeping reference samples. The quality control department shall evaluate, maintain and store Reference Standard substances.

B.1. 19.3 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.

B.1. 19.4 There shall be authorized and dated specifications which may be manufacturers own specifications for all materials and products. This should include test for identity, content, purity quality and / or functionality. Suppliers / manufacturers certificate may also be taken in place of in house testing. Functionality test shall be carried where ever identity test is not possible.

B.1. 19.5 No batch of the product is to be released for sale or supply until it has been certified to comply with the prescribed standards by the authorized person(s) that it is in accordance with the requirements of the standards laid down.

B.1. 19.6 Reference / retained samples from each batch of the products manufactured shall be maintained in a quantity which is at – least twice the quantity required to conduct all the tests performed on the active material and the product manufactured. The retained product shall be kept in its final pack.

B.1. 19.7 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 Head of the Quality Control Department before a product is released for sale or distribution.

B.1. 19.8 Quality Control personnel shall have access to production areas for sampling and investigation as appropriate.

B.1. 19.9 The Quality Control department shall conduct stability studies of the products to ensure and assign their shelf life at the prescribed conditions of storage. All records of such studies shall be maintained.

B.1. 19.10 The in-charge of Quality Control shall investigate all product complaints and records thereof shall be maintained.

B.1. 19.11 All equipments and testing procedures shall be validated before they are adopted for routine testing. Periodical validation of equipment and procedures shall be carried out.

B.1. 19.12 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.

B.1. 19.13 Pharmacopoeias, technical books, reference standards, reference spectra and other reference materials shall be available in the Quality Control Laboratory of the licensee.

B.1. 20 Specification

B.1. 20.1 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 specifications and

(h) Maximum period of storage before re – testing.

B.1. 20.2 For Product Containers and Closures:

B.1. 20.2.1 Suitable validated test methods, sample sizes, specifications, test methods, cleaning procedure and sterilization procedure, wherever indicated, shall be followed strictly

to ensure that these are not reactive, additive, adsorptive, 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.

B.1. 20.2.2 Whenever bottles are being used, the written scheduled of cleaning shall be laid down and followed. Where bottles are not dried after washing, they should be rinsed with de–ionized water or distilled water, as the case maybe.

B.1. 20.3 For in–process and bulk products:

Specifications for in – process material, intermediate and bulk products shall be available. The specifications should be validated and authenticated.

B.1. 20.4 For Finished Products

Appropriate specifications for finished products shall include :-

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

B.1. 21 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, batch number 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 equipment including cleaning, assembling, calibrating, sterilizing;

(g)Detailed stepwise processing instructions and the time taken for each step;

(h)The instructions for in – process controls with their limits;

(i)The requirements for storage conditions of the products, including the container, labeling and special storage conditions where applicable;

(j)Any special precautions to be observed;

(k)Packing details and specimen labels

B.1. 22 Packaging and Batch Processing Records

There shall be authorized 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 diagnostic preparation
(c) The pack size expressed in terms of the number or doses, weight or volume of the product in the final container;
(d) A complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications 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) A 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;
(i) Upon completion of the packing and labeling operation, a reconciliation shall be made between
number of labeling and packaging units issued, number of units labeled and packed and
excess returned or destroyed. Any significant or unusual discrepancy in the numbers shall be
carefully investigated before releasing the final batch.

B.1. 22.1 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 Master-Formula shall be designed to avoid transcription errors.

B.1. 22.2 Before any processing begins, check shall be performed and recorded that the equipment and workstation are clear of previous products, documents or materials not required for the planned process, are removed and that equipment is clean and suitable for use.

B.1. 22.3 During processing, the following information shall be recorded at the time each action is taken and, the record shall be dated and signed by the person responsible for the processing operations:

(a)Name of the product,

(b)Number of the batch being manufactured,

(c)Dates and time of commencement, of significant intermediate stages and of completion of production,

(d)Name and designation of the person responsible for each stage of production;

(e)Initials of the operator of different significant steps of production and where appropriate, of the person who checked each of these operations;

(f)The batch number and / or analytical control number as well as the quantities of each starting material actually weighed;

(g)Any relevant processing operation or event and major equipment used;

(h)A records of the in – process controls and the initials of the person (s) carrying them out, and the results obtained;

(i)The amount of product obtained after different and critical stages of manufacture (yield);

(j)Comments or explanations for significant deviations from the expected yield limits shall be given;

(k)Notes on special problems including details, with signed authorization, for any deviation from the master formula;

B.1. 23 Batch Packaging Records

B.1. 23.1 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.

B.1. 23.2 Before any packaging operations begins, checks 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 equipment is clean and suitable for use.

B.1. 24 Standard Operating Procedures (SOP's) and Records

B.1. 24.1 Receipt of Materials;

B.1. 24.1.1 There shall be written Standard Operating Procedures and records for the receipt of each delivery of raw, primary and printed packaging material.

B.1. 24.1.2 The records of the receipts shall include;

(a) The name of the material on the delivery note and the number of the 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.

B.1. 24.1. 3 There shall be written standard operating procedures for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

B.1. 24.1. 4 There shall be Standard Operating Procedures available for each instrument and equipment and shall be placed in close proximity to the equipment.

B.1. 24.2 Sampling

B.1. 24.2.1 There shall be written Standard Operating Procedures for sampling, which include the person(s) authorized to take the samples.

B.1. 24. 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,

B.1. 24.3 Batch Numbering.

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.

B.1. 24.4 Testing

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.

B.1. 24.5 Records of analysis.

B.1. 24.5.1 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.

B.1. 24.5.2 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, and hygiene;

(e) Environmental monitoring;

(f) Pest controls;

(g) Complaints;

(h) Recalls made;

(i) Returns received.

B.1. 25 Reference samples

Reference samples from each batch of the products manufactured shall be maintained in its final pack & in a quantity which is at least twice the quantity required to conduct all the tests performed

on the product manufactured. The reference samples shall be retained for till a period of 3 months after their expiry.

B.1. 26 Reprocessing And Recoveries.

B.1. 26.1 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 re–processing shall be validated.

B.1. 26.2 If the product batch has to be reprocessed, reprocessing 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.

B.1. 26.3 Recovery of product residue may be carried out, if permitted, in the master production and control records by incorporating it in subsequent batches or the product.

B.1. 27 Distribution records

B.1. 27.1 Prior to distribution or dispatch of given batch of a diagnostic preparation, 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 correct goods are only dispatched. Detailed instructions for warehousing and stocking of diagnostic preparation 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.

B.1. 27.2 Records for distribution shall be maintained in a manner that finished batch of a diagnostic kit / reagent is traced to end-user to facilitate prompt and complete recall of the batch, if and when necessary.

B.1. 28 Validation & Process Validation

B.1. 28.1 Validation studies shall be an essential part of Good Manufacturing Practices and shall be concluded as per the pre - defined protocols. These shall include validation of processing, testing and cleaning procedures.

B.1. 28.2 A written report summarizing recorded results and conclusions shall be prepared, documented and maintained.

B.1. 28.3 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 validated, prospectively or retrospectively.

B.1. 28.4 When any new master formula or method of preparation are 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 required quality.

B.1. 28.5 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 validated.

B.1. 29 Product recalls

B.1. 29.1 A prompt and effective product recall system of defective products shall be devised for timely information of all concerned stockiest, wholesalers, suppliers, and end users within the shortest period. The licensee may make use of both print and electronic media in this regard.

B.1. 29.2 The distribution records shall be readily made available to the persons designated for recalls.

B.1. 29.3 The designated person shall record a final report issued including a reconciliation between the delivered and the recovered quantities of the products.

B.1. 29.4 The recalled products shall be stored separately in a secured segregated area pending final decision on them.

B.1. 30 Complaints

B.1. 30.1 All complaints thereof concerning product quality shall be carefully reviewed and recorded 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.

B.1. 30.2 There shall be written procedures describing the action to be taken, recall to be made of the defective product.

B.1. 31 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 quality control operations of diagnostic preparations carried out at the licensed premises. It shall contain the following:

B.1. 31.1 General information –

(a) Brief information of the firm;

(b) Diagnostics 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 and mentioning the ways they are being manufactured;

(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;

(h) Details of punitive actions, if any, taken against the firm;

(i) Product details registered with Government institutions;

(j) Product details registered with foreign countries.

B.1. 31. 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 personal engaged in production;

(e) Personnel hygiene requirements, including clothing.

B.1. 31.3 Premises –

(a) Simple plan or description of manufacturing areas with the help of scale;

(b) Nature of construction and fixtures / fittings;

(c) Brief description of ventilation systems. More details should be given for critical areas with potential risks 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 systems (schematic drawings of systems), including sanitation

(f) Description of planned preventive maintenance programs for premises and of the recording system.

B.1. 31.4 Equipment

(a) Brief description of major equipment used in production and control laboratories (a list of equipment required);

(b) Description of planned preventive maintenance programs for equipment and of the recording system;

(c) Qualification and calibration, including the recording systems and arrangements for computerized systems validation.

B.1. 31.5 Sanitation –

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

B.1. 31.6 Documentation –

(a) Arrangements for the preparation, revision and distribution of necessary documentation for the manufacture;

(b) Any other documentation related to product quality that is not mentioned elsewhere (e.g. microbiological controls about air and water)

B.1. 31.7 Production –

(a) Brief descriptions of production operations using, wherever possible, flow sheets and charts specifying important parameters;

(b) Arrangements for the handling of starting materials, packaging materials, and 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.

B.1. 31.8 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.

B.1. 31.9 Loan license manufacture and licensee –

(a) Description of the way in which the Good Manufacturing Practices compliance of the loan licensee is assessed.

B.1. 31.10 Distribution, complaints and product recall

(a) Arrangements and recording system for distribution;

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

B.1. 31.11 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.

B.1. 31.12 Export of diagnostic preparations –

(a) Details of products exported to different countries;
(b) Complaints and product recall, if any.

B.2 SPECIFIC REQUIREMENTS FOR IN-VITRO DIAGNOSTIC REAGENTS / KITS

B.2.1 MINIMUM AREA REQUREMENT FOR IN VITRO DIAGNOSTIC MANUFACTURING UNIT

From manufacturing point of view, the in – vitro diagnostic reagents / kits are classified into five categories as follows:

(a) Liquid Chemistry
(b) Dry Chemistry
(c) Immuno-diagnostics
(d) Serology & Blood grouping reagents
(e) Molecular Diagnostics

Now the minimum area requirements are as follows:

ACTIVITY / DEPARTMENT	MINIMUM AREA REQUIREMENT
1) Raw Material Stores (Including cold Storage)	15 SM
2) Packing Material Stores (Both Primary & secondary P.M)	15 SM
3) Production Area (Including work in progress)	
a) Liquid Chemistry	10 SM
b) Dry Chemistry	10 SM
c) Immuno Diagnostics	10 SM
d) Serology & Blood groups	10 SM
e) Molecular Diagnostics	10 SM
4) Washing & Drying Area	15 SM
5) Quality Control / Quality Assurance	
a) Chemistry (Liquid & Dry both)	10 SM
b) Immuno Diagnostics & Serology	10 SM
c) Molecular Diagnostics	10 SM
6) Retained Sample Area	10 SM
7) Packaging / Assembly & Labeling Area	15 SM

8)	Finished Good Stores (Including cold Storage)	15 SM
9)	Change Room - Male	10 SM
10)	Change Room - Female	10 SM
11)	Production office / Record Room	10 SM
12)	Rest & Refreshment Area	10 SM
13)	Ancillary Area	10 SM

NOTE:

1) The area requirement mentioned here are the minimum requirement for specific activity and it does not include area for passage / corridor / staircase / guard room / office etc.

2) As for as the area requirement for production and quality- control are concerned, the manufacturer has to provide area for specific activity undertaken by him and not all of them. For e.g. If he is manufacturing only Liquid & Dry Chemistry types of products then minimum area for production & quality control will 20 SM and 10 SM respectively. The area requirement mentioned above for other activities are essential requirement and every manufacturer has to provide for the same.

3) Single cold storage area can be used for raw material, work in progress, retained / reference samples and finished product. In such a case the cold storage shall have separate demarcated space for each activity.

B.2.2 MINIMUM EQUIPMENTS REQUIRED FOR IN VITRO DIAGNOSTIC MANUFACTURING

B.2.2.1 Common Equipments

1. pH meter (separate for Q.C. and production)
2. Conductivity meter
3. Balance (separate for Q.C. and production)
4. Incubator (separate for Q.C. and production)
5. Oven
6. Refrigerator
7. Centrifuge
8. Autoclave
9. Pipettes / micro-pipettes
10. Appropriate Glassware

B.2.2.2 Specific Equipments

B.2.2.2.1 Dry Chemistry

1. DH area for filling
2. Mixing vessels
3. Appropriate weighing balances / filling machine
4. Spectrophotometer / Analyzer / Photometer

B.2.2.2.2 Liquid Chemistry

1. Appropriate mixing vessels and mixers
2. Dispensers / Filling machine
3. Appropriate weighing balances
4. DH room (if required)
5. Spectrophotometer / Analyzer / Photometer

B.2.2.2.3 Immunodiagnostics, serology & blood grouping kits

1. Dispensing / striping / coating equipment.
2. DH area for dry kits / components
3. Elisa Systems for companies manufacturing ELISA
4. Peptide Synthesis systems for companies doing in-house synthesis.
5. Laminar flow benches where ever required.

B.2.2.2,4 Molecular diagnostic kits

1. Thermal Cycler (for PCR based kits)
2. DH area for dry components
3. Dispensing / striping / coating equipment
4. Laminar flow bench
5. Electrophoresis equipments
6. Gel documentation equipments (U.V. Transiluminator) / or Elisa test system

B.2.3 PERSONNEL

B.2.3.2 MANUFACTURE : The manufacture of in vitro diagnostic products shall be conducted under active direction and personal supervision of competent technical staff consisting of at least one person who shall be whole time employee with a minimum experience of one year in the manufacture of in vitro diagnostic reagents / kits & possesses:

a) A Graduate degree in Science having one of the following as principle subject:

I) Microbiology
II) Biochemistry
III) Chemistry
IV) Biology (Zoology / Botany / life Science)

V) Biotechnology

OR

b) A Graduate degree in Medicine or Pharmacy from a recognised university or Institute

B.2.3.3 Testing / Quality control: The head of Quality Control shall be independent of the manufacturing & testing shall be conducted under active direction and personal supervision of competent technical staff consisting of at least one person who shall be a whole time employee with a minimum experience of one year in testing of in vitro diagnostic products and possesses:

a) A Graduate degree in Science having one of the following as principle subject:

I) Microbiology
II) Biochemistry
III) Chemistry
IV) Biology (Zoology / Botany / life Science)
V) Biotechnology

OR

b) A Graduate degree in Medicine or Pharmacy from a recognised university or Institute

B.2.4 LABELING REQUREMENT FOR IN VITRO DIAGNOSTIC REAGENTS / KITS

B.2.4.1 All the reagent used in the kit are required to be labeled individually, and a reagents list and their quantities should be disclosed on the container label of the kit.

B.2.4.2 Any specific instruction, precaution has to be incorporated for a particular test kit.

B.2.4.3 Expiry date disclosed on the outermost container should not exceed that of any component used in the kit.

B.2.4.4 Following details should occur on the label of the diagnostic reagent.

a) Generic name of the product.
b) Brand name, if any.
c) Volume / quantity / number of the test kit as the case may be.
d) Batch number, date of manufacture, Date of Expiry, manufacturer's name and address, license number, and maximum retail price (MRP).
e) Storage condition.
f) In case of a multi-component kit, each component should be labeled bearing name, Lot No, volume, manufacturing date, expiry date, storage condition & manufactures name and address. If there is constrain of space on smaller component then manufactures name & principal place of manufacture should be there instead of complete address.

B.2.4.5 Each kit pack should have a product literature providing details such as:

a) Component provided in the kit pack.
b) Materials required but not provided in the kit
c) How to perform the test. This should include information regarding sample collection, pre test
reagent preparation if any, test procedure and interpretation of results and limitation of the test.
d) Clinical significance of the test
e) Performance characteristics such as sensitivity, specificity, linearity etc.
f) Specific precautions to be taken while handling each type of kit.
g) Instructions for storage
h) Information regarding stability

B.2.5. ASSIGNMENT OF BATCH NUMBER TO THE DIAGNOSTIC REAGENTS / KITS.

B.2.5.1 Batch of a drug can be defined as a specific quantity of a drug or diagnostic reagent / kit that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture; and the same can be identified with a distinctive number allotted to it.

B.2.5.2 In case of a drug product it is simpler to assign a batch number to the product. However, for diagnostic reagent / kit many a times being a multi-component product, it is difficult to assign a specific batch number having traceability to all the components as different components are separately manufactured at different times, and part of them are used in formulating specific diagnostic reagent / kit.

B.2.5.3 Therefore it is important to maintain the identity of different component in a diagnostic kit. The identity of each of the component should be maintained on the container label of the kit by mentioning their lot numbers i.e. we assign a distinctive number to kit as whole and mentioned it on the container label alongwith the lot numbers of different components used in the final assembly of the kit. The records of issue of different Components for formulating a diagnostic reagent / kit have to be maintained in the batch sheet of the product.

B.2.6 MANUFACTURING DATE OF MULTI-COMPONENT DIAGNOSTIC KITS.

Diagnostic reagents / kits are of varied in nature. Some are simple solutions; one component reagent / kit or they may be of multi-component reagent / kits. In case of single component reagent manufacturing date can be fixed very easily, however in case of multi-component reagent, manufacturing dates of different component will naturally be different. Keeping this in mind it is more appropriate to adapt the date of final quality control of the assembled kit as the manufacturing date for the multi-component kits.

B.2.7 ASSIGNMENT OF SELF LIFE OF IN VITRO DIAGNOSTC REAGENT / KITS

B.2.7.1 The shelf Life of the Diagnostic Reagents / Kits will have to be fixed by the manufacturer on the basis of the stability studies conducted by them considering all the important protocols of tests of the diagnostic reagents / kits.

B.2.7.2 Mostly diagnostic tests are either storable between 2-8° C because of thermo-labile ingredients (mostly liquid reagents and dry enzymatic reagents) or between 2-30° C for most dry reagent (non-enzymatic and immuno-diagnostic).

B.2.7.3 No universally acceptable standard accelerated stability study protocol is available or possible for diagnostics products. This will vary with product, technology and nature of ingredients. However, from the experience of diagnostics companies world over alonwith correlating accelerated stability studies with real time data, the following protocol may be adapted

B.2.7.3.1

a) For 2-8° storage reagent 1-2 weeks stability at 37° C = 12 – 18 months at 2-8° C.
b) For 2-30° storage reagents 1-2 weeks stability at 45° C = 12-18 months at 30° C.

B.2.7.3.2 Accelerated stability protocol mentioned above or manufacturer's specific protocol should to be correlated with real time stability of the product. Real time data is the final proof of stability for diagnostic products.

B.2.8 MINIMUM INFORMATION TO BE PROVIDED IN THE ANALYTICAL REPORT (BATCH RELEASE CERTIFICATE)

An Analytical report (batch release certificate) must contain the following.

1. Name of the manufacturer with the address of the manufacturing premises.
2. Serial number / reference number / batch record number for the document and date of preparation.
3. Description of product including the generic name and brand name (if any).
4. Lot no., mfg. date, exp. date and pack size.
5. Recommended storage.
6. STP reference number.
7. Verification of labeling and packaging.
8. Test report for physical / chemical parameters and performance (as per STP).
9. Tested by --- with signature.
10. Signed for release by approved QC person.
11. Batch size
12. No of samples drawn for analysis.

B.2.9 NORMS FOR ADAPTING SPECIFICATION TO MAKE CONTROL PANEL FOR TESTING

B.2.9.1 No distinction between critical and non-critical products for adapting specification for control panel.

B.2.9. 2 For tests that can be quantified, known standards / secondary standards calibrated to international reference preparations (IRPs) either in-house, from the National Control Laboratory or from commercial sources (duly certified) must be used to assign sensitivity, linearity etc.

B.2.9.3 For test that cannot be quantified, characterized in-house panels representing weak, moderate and strong positive samples may be prepared, or a dilution series may be used and run in conjunction with previously approved batch.

B.2.9.4 These panels may be characterized wholly in-house (by testing with different approved products) or from international panels or from panels established / made available by the National Control Laboratory.

B.2.9.5 In addition positive and negative samples may be used and compared with previously approved batch.

B.2.9. 6 Further, if any specific blocking is made for a known interfering substance, such a sample / s may be included.

B.2.9.7 The number of samples / the type of samples, standards and panels will depend on product and batch size.