की एक श्रृंखला बनाई जाए और पिछले अनुमोदित बैच के साथ चलाया जाए । इन पैनलों को पूरी तरह से आंतरिक स्तर पर (विभिन्न अनुमोदित उत्पादों के साथ परीक्षण द्वारा) या अंतरराष्ट्रीय पैनलों से या राष्ट्रीय नियंत्रण प्रयोगशाला द्वारा स्थापित / उपलब्ध कराए गए पैनलों से बनाया जाए ।

(घ) इसके साथ ही धनात्मक और ऋणात्मक नमूनों की तुलना पिछले अनुमोदित बैच से की जाए ।

(ड़) और यदि एक ज्ञात व्यवधानकारी पदार्थ के लिए विनिर्दिष्ट ब्लॉकिंग की गई है तो ऐसे नमूने / नमूनों को शामिल किया जाए ।

(च) नमूनों की संख्या / नमूनों का प्रकार, मानक और पैनल, उत्पाद और बैच के आकार पर निर्भर करेंगे ।

[फा. सं. एक्स-11014/2/2006-डीएफक्यूसी]

देबाशीष पण्डा, संयुक्त सचिव

MINISTRY OF HEALTH AND FAMILY WELFARE

(Department of Health)

NOTIFICATION

New Delhi, the 25th February, 2008

G.S.R. 105(E).—The following draft of certain rules further to amend the Drugs and Cosmetics Rules, 1945, which the Central Government proposes to make, after consultation with the Drugs Technical Advisory Board, in exercise of the powers conferred by Section 12 and Section 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), is hereby published as required by the said sections for the information of all persons likely to be affected thereby, and notice is hereby given that the said draft rules will be taken into consideration after the expiry of a period of forty-five days from the date on which the copies of the Official Gazette in which this notification is published, are made available to the public;

Objections or suggestions, if any, may be addressed to the Secretary (Health), Ministry of Health and Family Welfare, Government of India, Nirman Bhavan, New Delhi-110011;

Any objection or suggestion which may be received from any person with respect to the said draft rules before the expiry of the period as specified above will be taken into consideration by the Central Government.

DRAFT RULES

1. (1) These rules may be called the Drugs and Cosmetics Rules, 2008.

   (2) They shall come into force after two years of their final publication in the Official Gazette.

2. In the Drugs and Cosmetics Rules, 1945 (hereinafter referred to as the said rules), in rule 76, after sub-rule (8), the following sub-rule shall be inserted, namely:-

"(9) The licensee manufacturing in-vitro diagnostics reagents or kits shall comply with the requirements of Good Manufacturing Practices and requirements of the premises, plant and equipments as laid down in Schedule M-IV."

3. In the said rules, after Schedule M-III, the following Schedule shall be inserted, namely. -

"SCHEDULE M-IV
(See Rule 76)

Good Manufacturing Practices and Requirements Of Premises, Plant and Equipment for In-Vitro Diagnostic Reagents or Kits

Note. - To achieve the objectives listed below, each licensee shall evolve appropriate methodology, system and procedure which shall be documented and maintained for inspection and reference; and the manufacturing premises shall be used exclusively for production of in -vitro diagnostic reagents/ kits and or no other manufacturing activity shall be undertaken therein.

PART – I

GENERAL REQUIREMENTS

1. Location and surroundings. -

The factory for manufacture of in- vitro diagnostic reagents or 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.

2. Buildings and premises.-

a) The buildings 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 and shall conform to the conditions laid down in the Factories Act, 1948 (63 of 1948).

b) 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 or 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 and 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-conditioned, where needed for the operations and items of diagnostic reagents / kits under production. The production and dispensing areas shall be well lighted and effectively ventilated. Wherever necessary, it should have provision for controlled temperature and 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 and rodents entering the premises. Open channels shall be avoided in manufacturing areas, but if inevitable these shall be shallow to facilitate cleaning and disinfection.

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.

4. Disposal of waste:-

(a) 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.

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

(c) 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.

5. Warehousing Area.-

(a) 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) 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.

(c) 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.

(d) 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.

(e) 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.

(f) Printed packaging materials shall be stored in safe separate and secure areas.

(g) Regular checks shall be made to ensure steps against spillage, breakage and leakage of containers.

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

6. Production area.-

(a) The production area shall be designed to allow the production in uni-flow and with logical sequence.

(b) 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.

(c) 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.

7. Ancillary areas.-

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

(b) 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.

(c) 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.

(d) 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.

8. Quality Control area.-

(a) 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.

(b) The design of the laboratory shall take into account the suitability of construction materials and ventilation. Separate air handling units and other requirements shall 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.

9. Personnel.-

(a) The manufacture shall be conducted under the active direction and personal supervision of competent technical staff having the prescribed qualifications and practical experience in production of diagnostic reagents / kits.

(b) 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.

(c) Personnel for Quality Assurance and quality control operations shall be suitably qualified and experienced.

(d) Written duties of technical and quality control personnel shall be laid and followed strictly.

(e) Each technical person shall be suitably trained to perform the assigned responsibilities. They shall be subjected to regular in-service training.

(f) Number of personnel employed shall be adequate and in direct proportion to the workload.

(g) 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.

10. Health, clothing and sanitation of workers.-

(a) 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. They shall be medically examined periodically, at least once in a year and 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) All 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.

(c) 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.

(d) 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.

(e) Direct contact shall be avoided between the unprotected hands of personnel and starting materials, intermediate or finished unpacked products.

(f) 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.

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

11. Manufacturing operations and controls.-

(a) 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) 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 number, batch size and stage of manufacture. Each label should be initialed and dated by the approved technical staff.

(c) Precautions against mix – up and cross – contamination.-

(i) 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;

(ii) 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;

(iii) 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;

(iv) 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;

(v) 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;

(vi) 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;

(vii) the manufacturing environment shall be maintained at the degree required of temperature, humidity and cleanliness;

(viii) authorized persons shall ensure change – over into specific uniforms before undertaking any manufacturing operations including packaging;

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

12. Sanitation in the manufacturing premises.-

(a) Dedicated and self – contained facilities shall be provided for the production of particular diagnostic preparation.

(b) 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.

(c) 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.

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

(i) specific areas to be cleaned and cleaning intervals;
(ii) cleaning procedure to be followed, including equipment and materials to be used for cleaning; and
(iii) personnel assigned to and responsible for cleaning operation.

(e) 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.

(f) Productions areas shall be well lit, particularly where visual on – line controls are carried out.

(g) Records of compliance in respect of sanitation shall be maintained for inspection.

13. Raw materials.-

(a) 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) All incoming materials and finished products shall be quarantined immediately after receipt or processing and 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.

(c) 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.

(d) Authorized staff shall be appointed by the licensee in this behalf, which may include personnel form the quality control department who 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.

(e) 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.

(f) Raw materials in the storage area shall be appropriately labeled. Labels shall be clearly marked with the following information:-

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

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

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

(iv) the manufacturing date, expiry date and re – test date.

(g) 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.

(h) Containers from which samples have been drawn shall be identified.

(i) 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.

(j) It shall be ensured that all the containers of raw materials are placed on the raised platforms or in steel racks.

14. Equipment.-

(a) 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 of the equipment shall be provided with a logbook wherever necessary.

(b) 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.

(c) 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.

(d) 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.

(e) Defective equipment shall be removed from production and quality control areas or appropriately labeled.

15. Documentation and records.-

(a) 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) Document and records shall contain the following characterizing:-

(i) documents shall be designed, prepared, reviewed and controlled, wherever applicable;

(ii) documents shall be approved, signed and dated by appropriate and authorized persons.

(iii) 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 and shall be regularly reviewed and kept up to date. Any alteration made in the entry of a document shall be signed and dated.

(iv) 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.

(v) 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.

16. Labels and other printed materials.-

(a) 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) 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).

(c) To avoid chance mix – up of printed and packaging materials, product leaflets, relating to different products, should be store separately.

(d) 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.

(e) Prior 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.

(f) Records 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.

(g) 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.

17. Quality assurance.-

(a) 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.

(b) The system of quality assurance appropriate to the manufacture of diagnostic preparations shall ensure the following:-

(i) the diagnostic preparations are designed and developed in a way that takes account of the requirements of Good Manufacturing Practices and other associated codes such as those of Good Laboratory Practices (GLP);

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

(iii) adequate controls on starting materials, intermediate products, and bulk products and other in – process controls, calibrations, and validations are carried out;

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

(v) the diagnostic preparations are not released for sale or supplied before authorized 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;

18. Self inspection and quality audit.-

(a) 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) 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.

(c) 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.

(d) Written instructions for self – inspection shall be drawn – up which shall include the following: -

(i) personnel;
(ii) premises including personnel facilities;
(iii) maintenance of buildings and equipment;
(iv) storage of starting materials and finished products;
(v) equipment;
(vi) production and in – process controls;
(vii) quality control;
(viii) documentation;
(ix) sanitation and hygiene;
(x) validation and revalidation programs;
(xi) calibration of instruments or measurement systems;
(xii) recall procedures;
(xiii) complaints management;
(xiv) labels control; and
(xv) results of previous self – inspections and any corrective steps taken.

19. Quality Control System.-

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

(c) 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.

(d) 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.

(e) 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.

(f) 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.

(g) 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.

(h) 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.

(i) Quality control personnel shall have access to production areas for sampling and investigation as appropriate.

(j) 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.

(k) The in-charge of quality control shall investigate all product complaints and records thereof shall be maintained.

(l) 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.

(m) 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.

(n) Pharmacopoeias, technical books, reference standards, reference spectra and other reference materials shall be available in the Quality Control Laboratory of the licensee.

20. Specification.-

(a) For raw materials and packaging materials, specification shall include the following:-

(i) the designated name and internal code reference;

(ii) reference, if any , to a pharmacopoeial monograph;

(iii) qualitative and quantitative requirements with acceptance limits;

(iv) name and address of manufacturer or supplier and original manufacturer of the material;

(v) specimen of printed material;

(vi) directions for sampling and testing or reference to procedures;

(vii) storage conditions and specifications; and

(viii) maximum period of storage before re – testing.

(b) For product containers and closures, specification shall include : -

(i) 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;

(ii) 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.

(c) 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.

(d) For finished products, appropriate specifications for finished products shall include:-

(i) the designated name of the product and the code reference;
(ii) directions for sampling and testing or a reference to procedures;
(iii) a description of the dosage form and package details;
(iv) the qualitative and quantitative requirements, with the acceptance limits for release;
(v) the storage conditions and precautions, where applicable and
(vi) the shelf – life.

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:-

(i) the name of the product together with product reference code relating to its specifications;

(ii) 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;

(iii) 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;

(iv) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;

(v) á statement of the processing location and the principal equipment to be used;

(vi) the methods, or reference to the methods, to be used for preparing the critical equipment including cleaning, assembling, calibrating, sterilizing;

(vii) detailed stepwise processing instructions and the time taken for each step;

(viii) the instructions for in – process controls with their limits;

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

(x) any special precautions to be observed;

(xi) packing details and specimen labels.

22. Packaging and batch processing records.-

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

(i) name of the product;
(ii) description of the diagnostic preparation;
(iii) the pack size expressed in terms of the number or doses, weight or volume of the product in the final container;
(iv) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications of each packaging material;
(v) reproduction of the relevant printed packaging materials, and specimens indicating where batch number and expiry date of the product have been applied;

(vi) 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;

(vii) a description of the packaging operation, including any significant subsidiary operations and equipment to be used;

(viii) details of in–process controls with instructions for sampling and acceptance; 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) 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.

(c) 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.

(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:-

(i) name of the product;

(ii) number of the batch being manufactured;

(iii) dates and time of commencement, of significant intermediate stages and of completion of production;

(iv) name and designation of the person responsible for each stage of production;

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

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

(vii) any relevant processing operation or event and major equipment used;

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

(ix) the amount of product obtained after different and critical stages of manufacture (yield);

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

(xi) notes on special problems including details, with signed authorization, for any deviation from the master formula.

23. Batch packaging records.-

(a) 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) 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.

24. Standard operating procedures (SOP's) and records.-

(a) Receipt of materials.-

(i) there shall be written standard operating procedures and records for the receipt of each delivery of raw, primary and printed packaging material;

(ii) the records of the receipts shall include the following:-

(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;

(iii) there shall be written standard operating procedures for the internal labeling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

(iv) there shall be standard operating procedures available for each instrument and equipment and shall be placed in close proximity to the equipment.

(b) Sampling.-

(i) there shall be written standard operating procedures for sampling, which include the person(s) authorized to take the samples;

(ii) 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.

(c) 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.

(d) 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.

(e) Records of analysis.-

(i) 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.

(ii) 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.

25. Reference samples.-

Reference samples from each batch of the products manufactured shall be maintained in its final pack and 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.

26. Reprocessing and recoveries.-

(a) 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) 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.

(c) 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.

27. Distribution records.-

(a) 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) 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.

28. Validation and process validation.-

(a) 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) A written report summarizing recorded results and conclusions shall be prepared, documented and maintained.

(c) 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.

(d) 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.

(e) 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.

29. Product recalls.-

(a) 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) The distribution records shall be readily made available to the persons designated for recalls.

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

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

30. Complaints.-

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

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:-

(a) General information. –

(i) brief information of the firm;

(ii) diagnostics manufacturing activities as permitted by the licensing authority;

(iii) other manufacturing activities, if any, carried out on the premises;

(iv) type of products licensed for manufacture and mentioning the ways they are being manufactured;

(v) number of employees engaged in the production, quality control, storage and distribution;

(vi) use of outside scientific, analytical or other technical assistance in relation to manufacture and analysis;

(vii) short description of the quality management system of the firm;

(viii) details of punitive actions, if any, taken against the firm;

(ix) product details registered with Government institutions;

(x) product details registered with foreign countries.

(b) Personnel. –

(i) organisational chart showing the arrangement for quality assurance including production and quality control;

(ii) qualification, experience and responsibilities of key personnel;

(iii) outline for arrangements for basic and in – service training and how the records are maintained;

(iv) health requirements for personal engaged in production;

(v) personnel hygiene requirements, including clothing.

(c) Premises. –

(i) simple plan or description of manufacturing areas with the help of scale;

(ii) nature of construction and fixtures / fittings;

(iii) 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;

(iv) special areas for the handling of the highly toxic, hazardous and sensitizing materials;

(v) brief description of water systems (schematic drawings of systems), including sanitation;

(vi) description of planned preventive maintenance programs for premises and of the recording system.

(d) Equipment.-

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

(ii) description of planned preventive maintenance programs for equipment and of the recording system;

(iii) qualification and calibration, including the recording systems and arrangements for computerized systems validation.

(e) Sanitation. –

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

(f) Documentation. –

(i) arrangements for the preparation, revision and distribution of necessary documentation for the manufacture;

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

(g) Production. –

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

(ii) arrangements for the handling of starting materials, packaging materials, and bulk and finished products, including sampling, quarantine, release and storage;

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

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

(h) Quality control. –

Description of the quality control system and of the activities of the quality control department. Procedures for the release of the finished products.

(i) Loan license manufacture and licensee. –

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

(j) Distribution, complaints and product recall.-

(i) arrangements and recording system for distribution;
(ii) an arrangement for the handling of complaints and product recalls.

(k) Self–inspection.-

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.

(l) Export of diagnostic preparations. –
(i) details of products exported to different countries;
(ii) complaints and product recall, if any.

PART-II

SPECIFIC REQUIREMENTS FOR IN-VITRO DIAGNOSTIC REAGENTS / KITS

Note:- The General Requirements as given in Part – I relating to Requirement of Good Manufacturing Practices for Premises and materials for in-vitro diagnostics reagents / kits shall be complied with, mutatis mutandis. In addition to these requirements, the following Specific Requirements shall also be followed.

1. Minimum area requirement for in-vitro diagnostic manufacturing unit.-

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

(i) liquid chemistry;
(ii) dry chemistry;
(iii) immuno-diagnostics;
(iv) serology and blood grouping reagents;
(v) molecular diagnostics.

(b) The minimum area requirements are as given in the Table below:-:

Sl. No.	Activity / Department	Minimum Area Requirement.
1)	raw material stores (Including cold storage)	15 SM
2)	packing material stores (both primary and secondary P.M)	15 SM
3)	production area (including work in progress)	
	i) liquid chemistry	10 SM
	ii) dry chemistry	10 SM
	iii) immuno diagnostics	10 SM
	iv) serology and blood groups	10 SM
	v) molecular diagnostics	10 SM
4)	washing and drying area	15 SM
5)	quality control / quality assurance	
	i) chemistry (liquid and dry both)	10 SM
	ii) immuno diagnostics and serology	10 SM
	iii) molecular diagnostics	10 SM
6)	retained sample area	10 SM
7)	packaging / assembly and 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 and 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. e.g. if he is manufacturing only liquid and dry chemistry types of products then minimum area for production and 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.

2. Minimum equipments required for in-vitro diagnostic manufacturing.-

(a) Common equipments

(i) pH meter (separate for Q.C. and production);
(ii) conductivity meter;
(iii) balance (separate for Q.C. and production);
(iv) incubator (separate for Q.C. and production);
(v) oven;
(vi) refrigerator;
(vii) centrifuge;
(viii) autoclave;
(ix) pipettes / micro-pipettes;
(x) appropriate glassware.

(b) Specific equipments

A. Dry Chemistry

(i) DH area for filling;
(ii) mixing vessels;
(iii) appropriate weighing balances / filling machine;
(iv) spectrophotometer / analyzer / photometer.

B. Liquid chemistry

(i) appropriate mixing vessels and mixers;
(ii) dispensers / Filling machine;
(iii) appropriate weighing balances;
(iv) DH room (if required);
(v) spectrophotometer / analyzer and photometer.

C. Immunodiagnostics, serology and blood grouping kits

(i) dispensing / striping / coating equipment;

(ii) DH area for dry kits / components;
(iii) Elisa Systems for companies manufacturing ELISA;
(iv) peptide Synthesis systems for companies doing in-house synthesis;
(v) laminar flow benches where ever required.

D. Molecular diagnostic kits

(i) thermal Cycler (for PCR based kits)
(ii) DH area for dry components
(iii) dispensing / striping / coating equipment
(iv) laminar flow bench
(v) electrophoresis equipments
(vi) gel documentation equipments (U.V. Transiluminator) / or Elisa test system

3. Personnal

(a) 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 and possesses the following qualification namely:-

A. A graduate in Science having one of the following as principle subject:

I) Microbiology;
II) Biochemistry;
III) Chemistry;
IV) Biology;
V) Biotechnology;

OR

B. A graduate in Medicine or Pharmacy from a recognized university or Institute.

(b) 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 the following qualification, namely:-

A. A graduate degree in Science having one of the following as principle subject:

I) Microbiology;
II) Biochemistry;
III) Chemistry;
IV) Biology;
V) Biotechnology;

OR

B. A graduate in Medicine or Pharmacy from a recognized university or Institute.

4. **Labeling requirement for in–vitro diagnostic reagents / Kits.-**

(a) 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) any specific instruction, precaution has to be incorporated for a particular test kits.

(c) Expiry date disclosed on the outermost container should not exceed that of any component used in the kit.

(d) Following details should occur on the label of the diagnostic reagent:-

(i) generic name of the product;
(ii) brand name, if any;
(iii) volume / quantity / number of the test kit as the case may be;
(iv) batch number, date of manufacture, date of expiry, manufacturer's name and address, license number, and maximum retail price (MRP);
(v) storage condition;
(vi) in case of a multi-component kit, each component should be labeled bearing name, lot no, volume, manufacturing date, expiry date, storage condition and manufactures name and address. If there is constrain of space on smaller component then manufactures name and principal place of manufacture should be there instead of complete address.

(e) Each kit pack should have a product literature providing details such as:-

(i) component provided in the kit pack;
(ii) materials required but not provided in the kit;
(iii) 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;

(iv) clinical significance of the test;
(v) performance characteristics such as sensitivity, specificity, linearity etc;
(vi) specific precautions to be taken while handling each type of kit;
(vii) instructions for storage;
(viii) information regarding stability.

5. Assignment of batch number to the diagnostic reagents / kits.-

(a) 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) 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.

(c) 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 along with 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.

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.

7. Assignment of self life of in- vitro diagnostic reagent / kits.-

(a) 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) 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).

(c) 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 along with correlating accelerated stability studies with real time data, the following protocol may be adapted:-

(i) for 2-8° storage reagent 1-2 weeks stability at 37° C = 12 – 18 months at 2-8° C;
(ii) for 2-30° storage reagents 1-2 weeks stability at 45° C = 12-18 months at 30° C.

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

(8) Minimum information to be provided in the analytical report (batch release certificate).-

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

(i) name of the manufacturer with the address of the manufacturing premises;

(ii) serial number / reference number / batch record number for the document and date of preparation;

(iii) description of product including the generic name and brand name (if any);

(iv) lot no., mfg. date, expiry date and pack size;

(v) recommended storage;

(vii) STP reference number;

(vii) verification of labeling and packaging;

(viii) test report for physical / chemical parameters and performance (as per STP);

(ix) tested by --- with signature;

(x) signed for release by approved QC person;

(xi) batch size;

(xii) no of samples drawn for analysis.

9. Norms for adapting specification to make control panel for testing.-

a) No distinction between critical and non-critical products for adapting specification for control panel.

b) 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.

c) 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. 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.

d) In addition positive and negative samples may be used and compared with previously approved batch.

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

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

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