DRUG REGULATORY AUTHORITY
OF PAKISTAN

Drugs(Licensing, Registering & Advertising), Rules, 1976

(As amended till October, 2022)

Drugs (LICENSING, REGISTERING & ADVERTISING) RULES, 1976

Notification No. S.R.O 145(I)/76, dated 12th February, 1976.- In exercise of the powers conferred by Section 41 of the Drugs Ordinance, 1976 (IV of 1976), the Federal Government is pleased to make the following rules, namely:-

Chapter 1

PRELIMINARY

1. Short title and commencement. (1) These rules may be called the Drugs (Licensing, Registering and Advertising) Rules, 1976.

(2) They shall come into force at once.

[1][**2. Definitions.** In these rules, unless there is anything repugnant in the subject or context-

[2][(*a*) Act means the Drugs Act, 1976 (XXXI of 1976);]

[3][(*aa*)] "active pharmaceutical ingredient" means a substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a pharmacologically active compound (ingredient);

(b) "airlock" means an enclosed space with two or more doors, which is interposed between two or more rooms of differing classes of cleanliness for the purpose of controlling the airflow between those rooms when they need to be entered and an airlock is designed for and used by either people or goods;

(c) "authorized person" means a person responsible for the release of batches of product for sale;

(d) "basic manufacture" means manufacture of drug from basic raw material to a produce which is ready for use as a starting material for the formulation of a finished drug or for repacking and such manufacture may involve chemical, biochemical, photochemical, microbial or such other processes or a combination of nay of such processes;

(e) "batch (or lot)" means a defined quantity of starting material, packaging material, or finish product processed in a single process or series of processes so that it could be expected to be homogeneous, in the case of continuous manufacture the batch must correspond to a defined fraction of the production, characterized by its

[1]Substituted by S.R.O. 470(I)/98, dated. 15.5.1998.
[2] Inst. By the SRO 662(I)/2005, dated. 25.6.2005
[3] Number re-lettered by SRO 662(I)/2005, dated. 25.6.2005

intended homogeneity, and to complete certain stages of manufacture it may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch;

(f) "batch number (or lot number)' means a distinctive combination of numbers and or letter which specifically indentifies a batch on the labels, the batch records, the certificates of analysis, and that permit the production history of the batch to be traced and revived;

(g) "batch numbering system: means a standard operating procedure describing the details of the batch numbering;

(h) "batch records" means all documents associated with the manufacture of a batch of bulk product of finished product showing a history of each batch of product and of all circumstances pertinent to the quality of the final product;

(i) "biological agents" means micro-organisms, including genetically engineered micro-organisms, cell cultures and endoparasites, whether pathogenic or not;

(j) "bulk product" means any product that has completed all processing stage upto, but not including, final packaging;

(k) "calibration" means the set of operations that establish, under specified conditions the relationship between values indicated by an instrument or measuring system for especially weighing, recording, and controlling, or the values represented by a material means, and the corresponding knon values of a reference standard and the limited for acceptance of the results of measuring;

(l) "clean area" means an area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce and or eliminate introduction, generation, and retention of contaminants within the area;

(m) "compounding" means scientific combination of two or more ingredients with a view to make a finished drugs;

(n) "consignment or delivery" means the quantity of starting material, or of a drug product, made by one manufacturer and supplied at one time in response to a particular request or order, a consignment may comprise one or more packages or containers and may include material belonging to more than one batch;

(o) "critical process" means a process that may cause variation in the quality of the pharmaceutical product;

(p) "cross-contamination" means the quantity of starting material, or of a drug product made by one manufacturer and supplied at one time in response to a particular request or order, a consignment may comprise one or more packages or containers and may include material belonging to more than one batch;

(q) "critical process" means a process that may cause variation in the quality of the pharmaceutical product:

(r) "cross-contamination" means a form set forth in Scheduel A;"

[4][*(s)* "formulation" means all operation involved in converting,--

(i) a drug into a final pharmaceutical dosage form ready for use as a finished drug including compounding, processing, formulation, filling packing, finishing labelling and other lik3e processes;

(ii) the materials into a medical device ready for use including formulating, molding, assembling, processing packing, finishing, labelling, sterilizing and other like process;]

(t) "good manufacturing practices for pharmaceutical products" means part of quality assurance which:--

(i) ensure that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization or product specification; and

(ii) diminish the risks, inherent in any "pharmaceutical production, including contamination, cross contamination and mix ups (confusion) that cannot be detected completely through the testing of final products;

(u) "half-finished product" means any material or mixture of materials that has to undergo further manufacture;

(v) "in-process control" means checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specifications and control of the environment or equipment may also be regarded as a part of in process control;

(w) "intermediate product" means partly processed material that must undergo further manufacturing steps before it becomes a bulk product;

(x) "large-volume parenterals" means sterile solutions intended for parenteral application with a volume of more than 100 ml in one container of the finished dosage form;

(y) "manufacture" means all operations of production, quality control, release, storage and the related controls;

(z) "manufacturer" means a company that carries out at least one step of manufacturer;

(aa) "marketing authorization" means a document, issued by the Drug Registration Board set up under the Drugs Act, 1976, as a certificate of drug registration;

(ab) "master formula" means a document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a

[4]Subs. by SRO 916(I)/2010, dated 30.9.2010

description of the procedure and precautions required to produce a specified quantity of a finished product as well as the quantity of a finished product as well as the processing instructions, including the in-process controls;

(ac) "master record" means a document or set of documents that serve as a basis for the batch documentation (blank batch record);

[5]*[(aca)* "medical device" means a disposable syringe, disposable set for collection or transfusion of blood or giving any infusion, canula, catheter, stent, auto-disable syringe or butterfly needle;]

(ad) "new drug" means a drug that has not been commonly sold or distributed to the public in Pakistan and is introduced for the first time;

(ae) "Ordinance" means the Drugs Ordinance, 1976 (IV of 1976);

(af) "packaging" means all operations, including filling and labelling which a bulk drug has to undergo in order to become a finished product;

Note: Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not the finally packaged, primary container.

(ag) "Packaging material" means any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment and packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contract with the product;

(ah) "pharmaceutical product" means any drug intended for human use or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form;

(ai) "processing instructions or procedures" means as defined in clause (ab) of this section;

(aj) "production" means all operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing and packaging to its completion as the finished product;

(ak) "Purity" means the degree to which other chemical or biological entities are present in any substance;

(al) Quality assurance" means the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use and so incorporates good manufacturing practices, Quality Control and other factors including product design and development and good laboratory practices;

[5]Clause (aca) inserted by SRO 916(I)/2010, dated 30.09.2010

(am) "quality control' means the part of good manufacturing practices concerned with sampling, specifications, and testing as well as the organization, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor finished products released for sale or supply until their quality has been judged to be satisfactory and it is involved in all decisions concerning the quality of the product;

(an) "quarantine" means status of starting or packaging materials intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing;

(ao) "reconciliation" means a comparison, making due allowance for normal variation between the amount of product or materials theoretically produced or used and the amount actually produced or used;

(ap) "recovery or blending" means the introduction of all or part of previous batches, or of redistilled solvents and similar products of the required quality into another batch at a defined stage of manufacture;

(aq) "repacking" means all operations involved in the transfer of a drug from a large container or packing into smaller containers or packing including filling, packing and labelling with a view to make it ready for retail sale or wholesale, but does not includes any compounding or processing with a view to formulate it in any dosage form;

(ar) "retail sale" means a sale other than wholesale;

(as) "reprocessing" means the reworking of all or part of a batch of product of an unacceptable quality from a refined stage of production so that its quality may be rendered acceptable by one or more additional operations;

(at) "returned product" means finished product sent back to the manufacturer or distributor;

(au) "schedule" means Schedule to these rules;

(av) "semi-basic manufacture" means manufacture from and intermediate substance of a drug to be used as a starting material for the formulation of a finished drug or to be sued for repacking;

(aw) "specification" means the requirements with which the products or materials used or obtained during manufacture must conform as specified in the Drugs (Specification) Rules, 1978;

(ax) "standard operating procedure" means an authorized written procedure indicating instructions for performing operations not necessarily specific to a given product or material but a more general nature such as equipment operation, maintenance and cleaning validation, cleaning of premises and environmental control

sampling and inspection, and certain standard operating procedures may be used to supplement product specific master and batch production documentation;

(ay) "starting material" means any substance used in the production of a pharmaceutical product but excluding packaging materials;

(az) "system" means a regulated pattern of interacting activities and techniques which are united to form an organized whole;

(ba) "validation" means the documented Act of proving that any procedure process, equipment, material, activity or system works correctly and actually leads to the expected result; and

(bb) "wholesaler" means sale to a person who purchases for the purpose of selling again and includes sale to a hospital or dispensary, or to medical, educational or research institute;

[6][*(bc)* "Lot Release" means an approval for the release into the market of specific lot of a biological drug, based upon certification that the lot meets the in-process controls and control tests on the final product;]

[7][*(bd)* "biological Drugs" mean medicinal products produced by biological systems and which require standardization by biological assays and include:--

(i) blood products including Plasma, Albumin, Clotting Factors, Factors VIII, IX, Mixed Clotting Factors Fractions Fibrinogens, Immunoglobulin;

(ii) immunological products including Antisera, Antitoxins, Monoclonal Antibodies, Specific Immunoglobulins;

(iii) in view diagnostics including Tubereulin, ALepromin, Histoplasin, Coccidiodin, Allergens, Allergen Extracts, Antibodies conjugated with isotopes for imaging studies, Antigens, Cytokines/Antibodies/Cells injected to elicit a biological response;

(iv) vaccines;-

a. bacterial including Live, Killed whole cell protein sub-unit, Polysaccharides or Glycoconjugates, Toxin derivatives, DNA;
b. viral including Live, inactivated, Sub-Unit, DNA.

(v) Toxins and venoms including Snake Venom;

(vi) Immunostimulants of biological origin including BCC;

(vii) Biotechnology products including DNA products, Recombinant Antibodies, Monoclonal Antibodies and derivatives, Gene Therapy products;

(viii) Insulin.]

[6]Added vide SRO No. 779(I)/2001, dated 5.11.2001
[7]Added vide SRO No. 779(I)/2001, dated 5.11.2001

Chapter 2

MANUFACTURE OF DRUGS FOR SALE

3. Types of licences to manufacture drugs. Licences to manufacture drugs shall be or the following types, namely:-

(i) licence to manufacture by way of basic manufacture;

(ii) licence to manufacture by way of semi-basic manufacture;

(iii) licence to manufacture by way of formulation;

(iv) licence to manufacture by way of repacking; and

(v) licence to manufacture for experimental purposes.

4. Manufacture on more than one set of premises. If drugs are manufactured on more than one set of premises, a separate application shall be made and a separate licence shall be issued in respect of each such set of premises.

5. Application for licence to manufacture drugs and fee therefore. (1) Application for the grant or renewal of a licence referred to in clauses (i) to (iv) of rule 3 shall be made in form 1 [8][or 1-A] to the Central Licensing Board addressed to its Secretary.

[9][(2) An application under sub-rule (1) shall be accompanied by the proper fee as specified in Schedule F];

[10][***];

[11][(2A) on receipt of an application for renewal of a licence any objection or shortcoming in the application observed by the Central Licensing Board may be notified to the applicant and he shall be given a time period of thirty days for rectification or completion of the application. In case he fails to rectify or complete the application within the specified period, the application may be rejected.]

(3) If the application for renewal of the licence is made after the expiry of the period of the validity of the licence, it shall be treated as a fresh application for the grant of licence.

(4) A fee of rupees one hundred shall be paid for a duplicate copy of the licence if the original is defaced, damaged or lost. Such copy of the licence shall bear the words “Duplicate Copy”.

(5) Any fee deposited under sub-rule (2) shall in no case be refunded.

[8]Inserted by SRO 691(I)/91, dated 29.7.1991
[9]Substituted sub-rule(2) vide SRO 959(I)/91, dated 26.9.1991
[10]Proviso omitted by SRO 277(I)/96, dated 21.4.1996.
[11] Added by SRO 431(1)/2005, dated 6.5.2005

[12][(6) For change of the name of a licencee, fee as prescribed under Schedule F for renewal of a licence shall be paid.]

6. Duration of a licence to manufacture drugs. A licence issued under this Chapter, unless earlier suspended or cancelled, be in force for a period of [13][five] years from the date of issue and may thereafter be renewed for periods of [14][five] years at a time:

[15][Provided that if application for renewal is made before the expiry of the period of validity of a licence, the licence shall continue in "force until" orders are passed on such application.

[16][Provided further that if an application for renewal is made after the expiry of the period of validity of a licence but within sixty days of its expiry, the licence shall continue to be in force on payment of additional surcharge of rupees five thousand for each day the application is delayed, and thereafter until order are passed on the such application.]

[17][Provided further that duration of a licence issued under rule 21 shall be two years unless earlier suspended or cancelled.]

[18][Provided further that the licence to manufacture drugs by way of formulation for medical devices, issued for the first time, shall be valid for a period for one year.]

7. Certificate of licence to manufacture. A licence to manufacture by way of basic manufacture, semi-basic manufacture, formulation or repacking, as the case may be, shall be issued in Form 2.

[19][8. Central Licensing Board. [(1) The Central Licensing Board shall consist of the following members, namely:--

(a) The Director Licensing, Drug Regulatory Authority of Pakistan, who shall be its *ex-officio* Chairman;

(b) One representative of Directorate of Quality Assurance and Laboratory testing;

(c) the Drug Controller or Chief Inspector of Drugs of the Provinces of Punjab, Sindh, Khyber Pakhtunkhwa and Balochistan;

(d) two experts having at least fifteen years working experience in production of drugs to be nominated by the Federal Government on recommendations of the Authority;

[12] Added by SRO 453(I)/2001, dated 8.6.2001
[13]Substituted the word "two" by SRO No. 534(I)/99, dated 29.4.1999.
[14]Substituted the word "two" by SRO No. 534(I)/99, dated 29.4.1999.
[15]Substituted "proviso" by SRO 285(I)/2002, dated 22.5.2002.
[16]Inst. By the SRO 431(I)/2005 dated 6.5.2005.
[17]Added by SRO 534(I)/99, dt 29.4.1999.
[18]Added by SRO 916(I)/2010, dated 30.9.2010
[19]Substituted vide SRO 944(I)/2007 dated 6th September, 2007.

(e) two experts of quality control or quality assurance having at least fifteen years experience of quality control or quality assurance in drugs to be nominated by the Federal Government on recommendations of the Authority;

(f) two professors of pharmacy from public or private universities in Pakistan;

(g) one law expert to be nominated by the Law, Justice and Human Rights Division who shall not be below BPS-19; and

(h) the Deputy Director General Licensing, Drug Regulatory Authority of Pakistan who shall be its ex-officio Secretary.]

(2) One representative each from Pharma Bureau, Pakistan Pharmaceuticals Manufacturing Association (PPMA), Pakistan Chemists and Druggists Association (PCDA) and consumer's organization may also attend the meeting of Licensing Board as observers to be nominated by the Federal Government.

(3) Except the *ex-officio* members, all members shall be nominated by Federal Government for a term of three years and shall be eligible for two terms only.

(4) The Central Licensing board may appoint its sub-committees consisting of its members for the scrutiny and evaluation of applications for the grant manufacturing licence or cases of GMP non-compliance referred by Federal Inspector of Drugs or panel of Inspectors or any authorized officer of the Drugs Control Administration.

(5) No member of the Central licensing Board shall be member of the Appellant board, Provincial Quality Control Board or Expert Committees constituted under Section 10 of the Act.

(6) the Central Licensing Board may co-opt any other person who is expert of any specialty for the disposal of relevant cases.

[20][(7) The Chairman himself or on the directions of the Chief Executive Officer of Drug Regulatory Authority of Pakistan, may call meeting of the Board.]

[21][(8) In the absence of Chairman, the Board may elect one of the members to preside over the meeting.]

(9) The quorum to constitute its meeting shall be four members including Chairperson.

(10) The Central licensing Board may authorize chairperson or any of its member for performing any specific functions of Board including the disposal of day-to-day business of Board through Sectary of the Central Licensing Board or any authorized officer of Drugs Control Administration.

(11) No Act or proceeding of the Central Licensing Board shall be invalid merely on the ground of the existence of any vacancy in, or any defect in the constitution of the Board.

[20]Subs by SRO 684(I)/2013, dated 29.7.2013

[21] Subs. By SRO 684(I)/2013, dated 29.7.2013.

(12) The Chairperson and the Secretary shall sign the manufacturing licence certificate. The Secretary or any authorized office shall conduct other correspondence on behalf of Central Licensing Board.

(13) The Central licensing Board shall fix the responsibility of offences before referring the case to the Drug Courts.

(14) The Central Licensing Board may cancel or suspend the manufacturing licence, or withdraw permission for manufacturing of a particular section of any firm on the availability of sufficient evidence on its own motion or on the recommendation of Drugs Registration Board, if any firm is involved in the manufacture and sales of spurious drugs.

The Drugs Registration Board may also recommend actions against the manufactures failed to comply with the GMP regulations [22][.]

(15) The Central Licensing Board may refer any case to the Biological Committee or veterinary Expert Committee for detailed examination and evaluation.

(16) The Central Licensing Board shall cancel or suspend the manufacturing licence or withdraw permission of any particular section or a firm after giving personal hearing or Show-Cause Notice to the concerned firm.

(17) The Central Licensing Board may appoint a panel of experts or inspectors of inspection of manufacturing units to submit its report to the Board.

(18) The Central licensing Board may extend the sealing periods upto three months for the licensed units on the requests of Federal Inspector of Drugs for the purpose of investigations provided that investigations shall be completed within three months by the Federal Inspector and complete case shall be submitted for the consideration of the Central Licensing Board:

Provided further that the Central Licensing Board may extend the sealing period upto the decision of the case by the Drugs Court in cases of unlicensed firms or where the license have been cancelled or suspended by the Central Licensing board:

Provided further that the Central Licensing Board shall record the reasons of such extensions.

(19) The Central Licensing Board may, in case of minor contravention, advise the firm for improvement or if considered necessary issued warnings and take other actions as deems fit for the purpose of improvement.

(20) The Central Licensing board shall follow the policy guidelines of the Federal government for the conduct business.]

9. Powers of the Central Licensing Board. (1) The members of the Central Licensing Board shall exercise all the powers of an Inspector without restriction as to area, and shall have the powers of a Provincial Inspector in relation to Section 30.

[22]Colon and Proviso omitted vide SRO 461(I)/2008, dated May 15, 2008.

(2) In the exercise of their powers the members of the Central Licensing Board shall follow the procedure prescribed for the Federal Inspector:

Provided that a member nominated by a Provincial Government may follow the procedure as laid down for a Provincial inspector.

10. Procedure of Central Licensing Board. (1) The Central licensing board may, before issuing a licence, cause the premises in which the manufacture is proposed to be conducted to e inspected by itself or by its sub-committee or by a panel of Inspectors or experts appointed by it for the purpose, which may examine all portions of the premises and the plant and appliances, inspect the process of manufacture intended to be employed and the means to be employed for standardizing, if necessary, and testing and analyzing substances to be manufactured and enquire into the professional qualifications of the technical staff employed.

(2) Where inspection under sub-rule (1) is carried out by a sub-committee or panel of experts or Inspectors appointed under the said sub-rule it shall forward to the Central Licensing board a detailed report of the result of the inspection [23][within a period of fifteen days].

(3) If the Central Licensing Board, after such further enquiry, if any, as it may consider necessary, is satisfied that the requirements of the rules have been complied with, it may issue a licence in Form 2.

(4) If the Central Licensing Board is not so satisfied, it shall reject the application and shall inform the applicant of the reasons for such rejection and of the conditions which must be satisfied before a licence may be issued [24][within a period of fifteen days].

(5) No application shall be entertained within three months of the rejection of an application under sub-rule (4).

(6) If after the expiry of three months but within six months of the rejection of an application under sub-rule (4), the applicant informs the Central licensing Board that the requirements of the rules have been fulfilled, the Board may if after causing a further inspection to be made, is satisfied that the conditions for the grant of a licence have been complied with, issue a licence and no further fee shall be required to be deposited for such an application.

(7) In case an application for licence to manufacture is made after the expiry of six months from the date of rejection of an application under sub-rule (4), such application shall be treated as a fresh application and full fee shall have to be deposited.

11. Special provisions regarding grant of a licence. (1) Where a manufacturer intends to manufacture a drug a part of the process of which is of specialized nature and would be uneconomical for him to conduct it, the Central Licensing Board may permit such process to be undertaken at another licensed premises specialized for this purposed, such subject to such conditions, if any, as may be specified in this behalf.

(2) If a person is conducting a part of the process of the manufacture on behalf of another manufacturer in accordance with the permission granted under sub-rule (1), and he is not

[23]Inserted by the SRO 662(I)/2005, dated 25.6.2005
[24]Inserted by the SRO 662(I)/2005, dated 25.6.2005

responsible for the quality of the final product the Central Licensing Board may not require him to establish an independent quality control laboratory for such products.

(3) if a person possesses, or applies for, more than one type of licences to manufacture drugs in the same premises, he may establish one Quality Control Department for the purpose of both the licences.

12. Cancellation or suspension of licences. (1) If a licensee does not comply with any of the conditions of a licence or violates any of the provisions of the Ordinance or the rules [25][****] the Central Licensing Board may, by an order in writing stating the reasons thereof, cancel a licence or suspend it for such period as it thinks fit, either wholly or in respect of some of the drugs to which it relates [26][:

Provided that in case of non-deposition of Central Research Fund, the manufacturing licence may be suspended till the settlement of the Fund.]

(2) The Central licensing Board, shall, before, cancelling or suspending a licence under sub-rule (1), [27][conduct an inquiry into the case and] provide an opportunity of being heard to the licensee.

(3) When a licence is cancelled or suspended, an entry to that effect shall be recorded on the licence.

(4) Licensee whose licence has been cancelled or suspended may appeal to the Appellate Board within sixty days of date of receipt of the decision of the Central licensing Board by the licensee and until the Appellate Board has given its order, the licence shall remain cancelled or suspended, as the case may be.

13. Renewal of a licence. On application being made for renewal, the Central Licensing Board may cause an inspection to be made, and if satisfied that the conditions of the licence and the rules are and will continue to be observed, shall issue a certificate of 1 renewal [28][****]

[Provided that if directed by the Central Licensing Board, the lciensee shall rectify the observations made during the inspection within a period which shall not be less than one month and more than three months from the date of receipt of orders in this regard and during this period the manufacturing in that particular area or the premises, as the case may be shall remain suspended and, until after re-inspection the Board grants renewal of licence, or otherwise rejects the application and inform the licensee accordingly.]

[29][14.******]

[25]Words "or fails to deposit the requisite amount of the Central Research Fund due from him" omitted by the SRO 662(I)/2005, dated 25.6.2005. Earlier inserted vide SRG No. 225(I0/86, dated 4th March, 1986.
[26] Full-stop and proviso added by the SRO 662(I)/20005, dated 25.6.2005.
[27]Inserted by the SRO 662(I)/2005, dated 25.6.2005.
[28]Words "or otherwise reject the application and inform the licensee accordingly" Omitted by the SRO 662(I)/2005, dated 25.6.2005. Earlier words inserted by the SRO 691(I)/91, dated 29.7.1991.
[29]Rules 14 omitted by the SRO 662(I)/2005, dated 25.6.2005

15. Conditions for grant of renewal of a licence to manufacture drugs by way of basic or semi-basic manufacture. (1) Before a licence to manufacture by way of basic or semi-basic manufacture is granted or renewed, the Central Licensing Board shall satisfy itself that the following conditions are complied with by the applicant, namely:-

(a) The applicant shall provide premises which shall suitable for intended use, in size and construction and shall be located in an area free from offensive and obnoxious odours and other possible sources of contamination;

(b) The applicant shall provide adequate space, plant and equipment for the manufacturing operations;

(c) The manufacture shall be conducted under the active directions and personal supervision of competent technical staff consisting of at least one person holding a degree in pharmacy (or chemical engineering or a masters degree in chemistry, with at least [30][ten] years experience in basic or semi-basic manufacturing from a university in Pakistan or any other institution, recognized by the Federal Government for the purposes of the [31][Act], [32][******]

(d) The applicant shall establish and independent Quality Control Department and maintain separate staff, premises and adequate laboratory equipment for carrying out tests of the strength, potency, quality and purity of the substances, being or to be used in the manufacture [33][and all in process control protocols and the required facilities shall be provided].

(e) The Quality Control Department shall be independent of the manufacturing units and its incharge shall be a whole-time employee of the manufacturer and shall possess a degree in pharmacy, [34][or chemical engineering or a masters degree in chemistry, with at least [35][ten] years' experience in basic or semi-basic manufacturing, from a University in Pakistan or any other institution recognized by the Federal Government for the purpose of Ordinance, [36][*****] and shall independent of the incharge of the manufacture (Production Units);

[30]Substituted vide SRO 1134(I)/2014 dated 17.07. 2014.
[31]Words subs. By the SRO 662(I)/2005, dated 25.6.2005.
[32]Words "medicine, science with chemistry or chemical engineering from a university in Pakistan or any other institution, recognized by the Federal Government for the purposes of the Ordinance, and shall possess qualifications and experience which, in the opinion of the Central Licensing Board, is appropriate and adequate for the manufacture and handling of the drug to be, or being, manufactured." By the SRO 662(I)/2005, 25.6.2005.
[33]Words added by SRO 662(I)/2005, dated 25.6.2005
[34] Words "medicine science with chemistry or chemical engineering from a university in Pakistan or any other institution, recognized by the Federal Government for the purposes of the Ordinance, and shall possess qualifications appropriate and adequate for the manufacture and handling of the drug to be , or being manufactured" substituted by the SRO 662(I)/2005, 25.6.2005.
[35]Substituted vide SRO 1134(I)/2014 dated 17.07. 2014.
[36]Words "or a degree in science with chemistry, or a degree in medicine, microbiology, pharmacology, of bacteriology from a university in Pakistan or any other institution recognized by the Federal Government for the purposes of Ordinance, as the Central Licensing board may deem fit for any particular unit" omitted by the SRO 662(I)/2005, dated 25.6.2005.

[37][Provided that for the testing of specialized products, relevant technical staff possessing a masters degree in microbiology or bacteriology shall be appointed.]

[38][(ea) Additional Staff for manufacturing and quality control having prescribed qualification and experience, shall be appointed and intimated to Licensing Authority, who shall lookafter the work qualified approved staff when not on duty.];

(f) The applicant shall ensure that--

(i) the manufacturing premises shall be maintained properly and shall, as far as possible, be orderly, lean and free from accumulated waste and vermin;

(ii) unhygienic practices such as eating and smoking shall not take place in any production or quality control area;

(iii) sufficiently clean, appropriately ventilated toilet facilities, including facilities for washing and rooms for changing cloths, shall be available for the use of manufacturing personnel where required;

(iv) hygienic garments shall be worn by all staff in processing and packaging areas;

(v) high standard of personnel hygiene shall be obverved by all persons concerned with production processes; and

(vi) no person known to be suffering from communicable disease or to be a carrier of such a disease and no person with open lesions or skin infection shall be engaged in production areas.

(g) The applicant shall provide—

(i) adequate facilities for first aid;

(ii) medical inspection of workers at the time of employment and periodical check up thereafter at least once a year;

(iii) facilities for vaccination and inoculation against the enteric or any other epidemic group of diseases; and

(iv) adequate precautions for safeguarding the health of the workers, including measures to avoid industrial accidents or diseases [39][:

[40][Provided that where a person possesses or applies for a licence to manufacture by way of basic and he also intends to conduct semi-basic manufacture of drugs, he may conduct such manufacture under the same license, subject to the approval of, and under such conditions as, the Central Licensing Board may specify.]

[37]Proviso added by the SRO 662(I)/20-05, dated 25.6.2005
[38]Inserted vide SRO 1134(I)/2014 dated 17.07. 2014.
[39]Substituted for “full stop” by SRO 371(I)97 dated 21.5.1997
[40]Added “proviso” by SRO 371(I)/297, dated 21.5.1997

16. Conditions for the grant or renewal of licence to manufacture drugs by way of formulation. Before a licence to manufacture drugs by way of formulation is granted or renewed, the Central Licensing board shall satisfy itself that the following conditions are being complied with by the applicant namely:--

(a) The factory premises shall comply with the conditions specified in Schedule B.

(b) The applicant shall provide adequate space, plant and equipment for the manufacturing operations, the minimum space, plant and equipment for various operations are specified in Schedule B (1).

[41][(bb) "An applicant, for registration of insecticides, pesticides and household disinfectants shall in addition to the conditions specified in Schedule BN and Schedule B-1 comply with the conditions specified in Schedule B-1, A".]

(c) The manufacture shall be conducted under the active directions and personal [42][being the production incharge] supervisions of competent technical staff consisting of at least one person who is a whole-time employee and who has—

(i) a degree in pharmacy from a university in Pakistan or any other institution recognized by the Federal Government for the purpose of the Ordinance and has at least [43][ten years] of practical experience in the manufacture of [44][type of drugs to be manufactured]; or

(ii) a [45][masters] degree in science with chemistry or pharmaceutical chemistry as the principal subject who, [46][******] has not less than [47][fifteen] years practical experience in the manufacture of drugs intended to be manufactured knowledge of pharmacy which, in the opinion of the Central Licensing Board, is adequate for the purposes; or

(iii) any foreign qualification the quality and content of the training of which are comparable with those described in sub-clause (i) or sub-clause (ii) and is approved for the purposes of this sub-rule by the Central Licensing board:

Provided that the Central licensing Board may, in the case of manufacture of drugs included in Schedule C, permit the manufacture of such drugs under the active direction and personal supervision or a person holding a degree in medicine or veterinary sciences of a university of Pakistan or any other insituti8on recognized by the Federal Government, with at least three years experience in the manufacture, testing and analysis of biological products which are intended to be produced:

[41]Inserted "clause (bb)" vide SRO No. 268(I)/83, dated 20.3.1983.
[42]Words inst. By the SRO 662(I)/2005, dated 25.6.2005.
[43]Substituted vide SRO 1134(I)/2014 dated 17.07. 2014.
[44]Substituted the word "drugs" by SRO 470(I)/98, dated 15.5.1998.
[45]Words insert by the SRO 662(I)/2005, dated 25.6.2005.
[46]Words "for the time being, is working as incharge of a licensed pharmaceutical manufacturing unit," omitted by the SRO 662(I)/2005, dated 25.6.2005.
[47]Substituted vide SRO 1134(I)/2014 dated 17.07. 2014.

Provided further that the Central licensing Board, may, in the case of manufacture of disinfectant fluids, insecticides, liquid, paraffin, medicinal gases, non-chemical contraceptives, plaster of paris, surgical dressing or chemical for the manufacture of which the knowledge of pharmacy or pharmaceutical chemistry is not essential, permit manufacture of the drug under the active direction and personal supervision of competent staff who, [48][****] has in the opinion of the Central Licensing Board, adequate knowledge and experience in the manufacture of the drugs(s) to be produced .

[49][Provided further, that a person already approved by the Central Licensing Board as the production incharge of a pharmaceutical firm shall continue to the technical supervisor of that firm for the purpose of this rule.]

[50][Provided that if a firm has more than one section, the manufacture shall be conducted under the active directions and personal supervision of competent technical staff which shall be at least one for each section and who shall be a whole-time employee with [51][……] experience[52][of not less than three years].]

(d) The applicant shall establish and independent Quality Control Department and maintain separate staff, premises and adequate laboratory equipment for carrying out tests of strength, quality and purity of the substances being or to be used in the manufacture.

(e) The Quality Control Department shall be independent of the manufacturing unit and its incharge shall be a whole time employee of the manufacturer and shall possess a degree in pharmacy, or as degree [53][masters] in science with chemistry or a degree in medicine or pharmacology (for pharmacological testing) or a degree in microbiology for microbiological testing) and has [54][[55][ten] years experience in testing of types of drugs intended to be manufactured]:

Provided that in the case of drugs specified in Schedule C, the Central Licensing Board may allow the applicant to make arrangements with some other institution approved by the Central Licensing board for such tests to be regularly carried out on his behalf by that institution.

[56][Provided further that there shall be a separate incharge for the in process control of the drugs being manufactured who shall; possess a degree in pharmacy or a masters degree in chemistry, with sufficient experience.]

[48]Words omitted by SRO 1362(I)/96, dated 28.11.1996
[49]Proviso added by SRO 1362(I)/96, dated 28.11.1996
[50]Proviso added by the SRO 662(I0/2005, dated 25.6.2005.
[51]Omitted vide SRO 1134(I)/2014 dated 17.07. 2014.
[52]Added vide SRO 1134(I)/2014 dated 17.07. 2014.
[53]Inserted by SRO 662(I)/2005, dated 25.6.2005.
[54]Substituted for the words “sufficient experience in testing of drug” vide SRO No. 470(I)/98, dated 15.5.1998.
[55]Substituted vide SRO 1134(I)/2014 dated 17.07. 2014.
[56]Proviso added by the SRO 662(I)/2005, dated 25.6.2005

[57][(f) An application for site verification or approval of the layout plan or an application for extension or revision of layout plan, as the case may be, shall accompanied with a fee as prescribed under Schedule F.]

[58][(g) additional Staff for manufacturing and quality control having prescribed qualification and experience, shall be appointed and intimated to Licensing Authority, who shall lookafter the work of qualified and approved staff when not on duty.]

17. Licence to manufacture drugs by way of repacking. (1) A licence to manufacture drug by way of repacking is required foil the repacking of such drugs, and under such conditions, as are specified in Schedule D.

(2) Where a person possesses or applies for a licence to manufacture by way of formulation and he also intends to conduct repacking of drugs, he may conduct such repacking under the same licence subject to the approval of, and under such conditions as, the Central Licensing Board may specify.

[59][(3) An application for repacking of a drug specified it Schedule D shall be accompanied with a fee as prescribed under Schedule F and such permission shall be valid for a period of five years only.]

18. Condition for the grand or renewal of a licence manufacture drugs by way of repacking. Before a licence manufacture drugs by way of packing is granted or renewed, the Central Licensing Board shall satisfy itself that the following conditions are complied with the applicant, namely:--

(a) adequate space and equipment shall be provided;

(b) repacking operation shall be carried out under hygienic conditions and under supervision of technical staff provided for in clause (c) of rule 16;

(c) adequate arrangements shall be provided for carrying out the tests for strength potency, quality and purity of the drugs to be repacked; [60][and

(d) all in process control protocols and required facilitates shall be provided.]

19. Conditions of licence to manufacture, by way of basic manufacture, semi-basic manufacture, formulation and repacking of drugs. (1) A licence to manufacture by way of basic, semi-basic manufacture, formulation or repacking of drugs shall be subject to the conditions stated therein, if any, and to the further condition that the licensee shall continue to maintain conditions on the basis of which he was granted a licence.

[57]Added by SRO 877(I)/2000, dated 9.12.2000
[58]Added vide SRO 1134(I)/2014 dated 17.07. 2014.
[59]Added by SRO 877(I)/2000, dated 9.12.2000
[60]Added by the SRO 662(I)/2005, dated 25.6.2005

(2) The licence shall be kept on the licenced premises and shall be produced at the request of any member of the Central Licensing Board or of Provincial Quality Control Board or an Inspector.

(3) Any charge in the expert staff or signification alteration in the licensed premises or equipment shall be immediately notified to the Central licensing Board.

(4) The licensee shall maintain in the inspection book provided by the Central Licensing Board at the time of the issuance of the licence on which a member of the said Board or of a Provincial Quality Control Board or an inspector shall record proceedings of each of his visits, his impressions and the defect or irregularities noticed, if any, by him and such inspection book shall be signed by him as well as the licensee or his authorized agent.

(5) If any defects or irregularities are recorded in the inspection book under sub-rule (4), the manufacturer shall take steps to remove such defects or irregularities.

[61][(5-A) A fee of one thousand rupees shall be paid for a duplicate inspection book if the original is defaced, damaged or lost. Such book shall bear the word 'duplicate' and shall be issued after pasting the copies of the last three inspection reports available on record.]

(6) A licensee who for any purpose is engaged in the culture or manipulation of pathogenic spore-bearing micro-organism shall provide, to the satisfaction of the Central Licensing Board, separate laboratories, utensils and apparatus required for the culture or manufacture of any other substance.

(7) The licensee shall comply with the provisions of the Ordinance and the rules and with such further requirements, if any, as may be specified in any rule subsequently made in this behalf or any other condition that may be imposed at the time of grant of a licenced in the special circumstances of each case.

(8) The licensee shall allow any member of the Central Licensing Board or of a Provincial Quality Control board or an Inspector to enter, with or without prior notice, any premises and to inspect the plant and the process of manufacture and means employed in standardizing and testing the drugs and to take samples for test and analysis.

(9) The licensee shall allow any member of the Central licensing Board or of a Provincial Quality Control Board or an Inspector to inspect all registers and records marinated under these rules and to take samples of the manufacture drugs and shall supply to such member or Inspector such information as he may require for the purpose of ascertaining whether the provisions of the Ordinance and the rules have been observed.

(10) The licensee shall, on demand, furnish to the Central Licensing Board or the Provincial Quality Control Board or to such authority as the Central licensing Board may direct, from every batch of a drug, or from such batch or batches of drugs as it may from time to time specify, a sample for examination and, if required, furnish full protocols of the tests which have been applied.

[61]Inserted new "sub-rule (5-A)" by SRO 877(I)/2000, dated 9.12.2000

(11) If the Central licensing board or a Provincial Quality Control Board so directs [in writing with reasons to be recorded therein after providing an opportunity of being heard], the licensee shall not sell or offer for sale any batch of a drug in respect of which a sample is, or protocols are, furnished under clause (10) until a certificate authorizing the sale of the batch of such drug has been issued to him by or on behalf of the Central Licensing Board or the Provincial Quality Control Board, as the case may be.

(12) The licensee shall on being informed by the Central Licensing Board or a Provincial Quality Control Board that any part of any batch of a drug has been found not to conform with the requirements of the Ordinance or the rules and on being directed so to do, with the remainder of the batch of such drug from sale and, so far as may in the particular circumstances of the case be practicable, recall all issues already made from the batch and dispose it of in such manner as may be directed by the said Board.

(13) No drug manufactured under a licence shall be [stored at the licensed premises] unless [by the 30th June and 31st December each year whichever is immediately after the annual financial closing of the company] precautions necessary for preserving its properties have been observed through the period after manufacture.

[62][(13-A) The licensee or his authorized agent shall issue a warranty in form 2A for any drug sold by him for the purpose of resale or distribution.]

[63][(14) The licensee shall [64][by the 30th June and the 31st December each year whichever is immediately after the annual financial closing of the company] contribute one percent of his gross profit before deduction of income-tax towards the Central Research Fund to be maintained by the Federal Government and utilized by it in accordance with the Drugs (research) Rules, 1978]

Provided that the Central Licensing Board may allow a portion of such contribution to be spent by the firm itself for research and development of new drugs or for establishing research laboratories when it is fully satisfied that such expenditure will be utilized for the said purpose effectively and properly.

[65][*Explanation.* In this sub-rule, "profit" means gross profit before payment of income tax or other tax.]

[66][(14-A) The contributions made towards the Central Research Fund under sub-rule (14) shall be kept in such bank as the Federal Government may specify and shall be utilized in accordance with the Drugs (Research) Rules, 1978].

[67][(15) The licensee shall, on or before the 31st July each year, submit a duly signed profit and loss statement as each year, submit a duly signed profit and loss statement as per

[62] Inserted by SRO 88(I)/77, dated 15.1.1977
[63] Substituted vide SRO 620(I)/88, dated 26th April, 1988
[64]Inserted by SRO 1193(I)/96, dated 15.10.1996.
[65]Added by SRO 225(I)/86, dated 4.3.1986.
[66]Added by SRO 346(I)/79, dated 11.4.1979.
[67]Added vide SRO 225(I)/86, dated 4.3.1986.

"proforma" given in Form 1 of Schedule A along with an evidence of deposit of 1 percent of profit towards the Central Research Fund.]

20. Additional conditions of licence to manufacture drugs by way of formulation. A licence to manufacture drugs by way of formulation shall, in addition to the conditions laid down in rule 19, be subject to the following further conditions, namely:--

(a) The licensee shall comply with the requirements and the conditions in respect of good practices in the manufacture and quality control of drug, as specified in Schedule B-III.

(b) The licensee shall record in Schedule B0-III the particulars of manufacture of each batch of drugs manufactured by him and shall retain such records, in the case of a substance for which expiry date is fixed for a period of [68][one year] from the expiry of such date [69][***]

(c) The licence shall either in his own laboratory or where so authorized under the proviso to clause (e) of rule 10, in any other laboratory approved by the Central Licensing Board, test such batch of the raw materials used by him for the manufacture of drugs and also each batch of the final drug, shall maintain records showing the particulars in respect of such tests as specified in Schedule B-III and shall retain such records, in the case of a substance for which expiry date is fixed, for a period of two years from the expiry of such date and, in the case of other substance, for a period of five years from the date of manufacture.

[70][**20A. Contract manufacture**. — (1) Manufacture or analysis, through contract, either for local sale or export purpose, shall be permissible by contract giver if:-

(a) a licenced pharmaceutical manufacturer having licence to manufacture by way of formulation; or

(b) an importer for its already registered drug products in Pakistan for permission from finished drug product import to contract manufacturing by a licenced pharmaceutical manufacturer; or

(c) a foreign pharmaceutical company (manufacturer or marketing authorization holder) having drug sale licence in Pakistan for their research, innovator, originator drug products or drug products already registered for sale by any of reference regulatory authorities adopted by the Registration Board; or

(d) licenced pharmaceutical manufacturing unit, which is granted a certificate by Registration Board to the effect that the unit is unable to maintain its production or output level due to reasons beyond its

[68]Subs. By the SRO 662(I)/2005, dated 25.6.2005.
[69]Words omitted by the SRO 662(I)/2005, dated 25.6.2005.
[70]Substituted vide SRO 1347(I)/2021, dated 15.10.2021.

control, including but not limited to repair or upgradation requirements:

Provided that the contract manufacturing under this clause shall be for a period of thirty months extendable for a further period of twenty-four months by the Registration Board on valid grounds.

(2) The provisions of sub-rule (1) shall be subject to the following conditions, namely: -

(a) the provisions of rule 26, 27, 28, 29 and 30 shall *mutatis mutandis* apply;

(b) contract manufacturing shall be allowed between human to human and veterinary to veterinary drugs only;

(c) contract manufacturing of controlled drugs (narcotic drug or psychotropic substances or precursor chemicals) shall not be allowed;

(d) contract manufacturing shall also be subject to the conditions laid down in Schedule-H.]

21. Licence to manufacture drugs for experimental purposes. (1) If a person intending to manufacture a drug for experimental purposes does not hold a licence to manufacture drugs, he shall before commencing such manufacture, apply in Form 3 for the grant or renewal of a licence to the Central Licensing Board addressed to its Secretary.

(2) An application under sub-rule (1) shall be countersigned by the head of the institution in which, or the director or manager o the firm or company by which, the drug will be manufactured.

(3) Licence for the manufacture of drugs for experimental purposes shall be in Form 4.

22. Conditions of licenced to manufacture drugs for experimental purposes. A licence issued under rule 21 shall be subject to the following conditions, namely:-

(a) That licensee shall use the drugs manufactured under the licence exclusively for experimental purposes and shall carry on the manufacture and experimental work at the place specified in the licence.

(b) The licensee shall allow a member of the Central Licensing Board or of a Provincial Quality control Board or an Inspector to enter, with or without notice, the premises where the drugs are manufactured and to satisfy himself that the manufacture is being conducted for experimental purposes.

(c) The licensee shall comply with such further requirements, if any, as may be specified under any rule subsequently made.

23. Labelling of drugs manufactured for experimental purposes. (1) Any drug manufactured for experimental purposes shall be kept in containers bearing labels indicating the purpose for which it has been manufactured.

(2) If the drug manufactured for experimental purposes is supplied by the manufacturer to any other person, the container shall bear a label on which should be stated the name and address of the manufacturer, the accepted scientific name of the drug, if known, or, if not known, a reference which will enable the drug to be identified and the purpose for which it has been manufactured.

Chapter 3

REGISTRATION OF DRUGS

[71][**24. Registration Board.** (1) The Registration Board shall consist of following members, namely:-

[72][(a) the Director Pharmaceutical Evaluation and Registration, Drug Regulatory Authority of Pakistan who shall be its *ex-officio* Chairman;

(b) one representative of Directorate of Biological Drugs;

(c) one representative of Directorate of Medical Devices and Medicated Cosmetics;

(d) one representative of Directorate of Quality Assurance and Laboratory Testing;

(e) the Director, Drug Testing laboratory of the Punjab, Sindh, Khyber Pakhtunkhwa and Balochistan;

(f) one expert having at least fifteen years experience in the field of veterinary medicine to be nominated by the Federal government on recommendations of the Authority;

(g) one expert having at least fifteen years experience in the field of biological to be nominated by the Federal government on recommendations of the Authority;

(h) one expert having at least fifteen years experience in the field of pharmacology to be nominated by the Federal Government on recommendations of the Authority;

(i) one expert having at least fifteen years experience in the field of hospital pharmacy to be nominated by the Federal Government on recommendations of the Authority;

(j) one physician having at least fifteen years experience to be nominated by the Federal government on recommendations of the Authority;

(k) one expert having at least fifteen years working experience in manufacturing of drugs to be nominated by the Federal Government on recommendations of the Authority;

(l) one representative of Intellectual Property Organization of Pakistan (IPO-Pakistan);

[71]Subs. Vide SRO 944(I)/2007, dated 6th September, 2007, earlier subs. By SRO 732(I)/78, dated 7th June, 1978.
[72]Subs. By SRO 684(I)/2013, dated 29.7.2013.

(m) one law expert to be nominated by the Law, Justice and Human Rights Division who shall not be below BPS-19; and

(n) the Deputy Director General, Registration, Drug Regulatory Authority of Pakistan who shall be its ex-officio Secretary.]

(2) One representative each from Pharma Bureau, Pakistan Pharmaceuticals Manufacturing Association (PPMA), Pakistan Chemists and Druggists Association (PCDA) and consumer's organization, may also attend the meeting of Registration Board observers to be notified by the Federal government.

(3) Except the *ex-officio* members, all members shall be nominated by the Federal government fo a term of three years and shall be eligible for two terms only.

(4) Registration board may appoint sub-committees consisting of its members for the scrutiny and evaluation of applications for the grant of registration, or cases referred by the Federal Inspector of Drugs, Assistant Drugs Controllers or any authorized officer of Drugs Control.

(5) No member of the Registration Board shall be member of the Appellate Board, Provincial Quality Control Board or Expert Committees constituted under Section 10 of the Act.

(6) The Registration Board may co-opt any other person who is expert of any specialty for the disposal of relevant cases.

[73][(7) The Chairman himself or on directions of the Chief Executive Officer of Drug Regulatory Authority of Pakistan, may call meeting of the Board.]

[74][(8) In the absence of Chairman, the Board may elect one of the Members to preside over the meeting.]

(9) The quorum to constitute a meeting shall be four members including Chairperson.

(10) The Registration Board may authorize Chairperson, or any of its member for performance of specific functions of Board including the disposal of day to day business of Board through the Secretary of the Registration Board.

(11) No act or proceeding of the Registration board shall be invalid merely on the ground of the existence of any vacancy in, or any defect in the constitution of the Board.

(12) The Secretary, or any officer authorized by the Chairperson, shall sign the Registration certificate or letter or other correspondence on behalf of Registration Board.

[75][(13) x x x x x]

[76][(14) x x x x x]

[73]Sub-rule (7) subs. By SRO 684(I)/2013, dated 29.7.2013.
[74]Sub-rule (8) subs. By SRO 684(I)/2013, dated 29.7.2013.
[75]Sub-rule (13) omitted by SRO 461(I)/2008, dated 16.5.2008.

(15) The Registration Board may refer any case, of registration application, to the Biological Committee, veterinary Expert Committee, or any other committee for detailed examination evaluation, enquiry or recommendations.

[77][(16) x x x x x]

(17) The Registration board shall cancel or suspend the registration of drugs after giving personal hearing or show-cause notice to the concerned firm.

[78][Sub-rules (18) to (24) omitted by the SRO 461(I)/2008, dated 16.5.2008.]

25. Powers of Registration Board. The members of the Registration Board shall exercise all the powers of Inspector without restriction as the area, and shall have the powers of a Provincial Inspector in relation to Section 30.

26. Application for registration of drugs and feels thereof.[79][(1) An application for registration of a drug for the local manufacture of a drug substance having the same active ingredient or salt thereof, therapeutic use, dosage form and route of administration that has already been approved by the Registration board and had not been withdrawn from sale for reasons of safety or effectiveness, shall be made in Form 5, for imported drugs on Form 5-(A), for new drug molecule on Form 5-D for a new drug molecule having valid patent within Pakistan on Form 5-D and an electronic copy shall also by provide in the Form of a CD in the Microsoft Word format in duplicate to the Registration board addressed to its Secretary, and separate application shall be made for each drug][80][or on Form 5-F(Common Technical Document) as notified by the Drug Regulatory Authority of Pakistan; and the Registration Board may issue necessary explanations and exemptions in this regard if needed;]

[81][Provided that an applicant may submit registration application on existing forms (Form 5 or 5-A or 5-D, or 5-E) for a period of 6 months, which may be extended, on justifiable reasons, for further period as determined by DRAP, after notification of Form 5-F by DRAP.]

(2) The applicant shall furnish such further information and material as may be required by the Registration board for the proper evaluation of the [82][new drug molecule]

(3) Omitted by the SRO 662(I)/2005, date 25.6.2005.

(4) Omitted by the SRO 662(I)/2005, dated 25.6.2005.

(5) A fee of rupees [83][thousand] shall be paid for a duplicate copy of the certificate of registration if the original is defaced, damaged or lost, and such copy of the certificate shall bear the words "DUPLICATE COPY".

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[76]Sub-rule (14) omitted by SRO 461(I)/2008, dated 16.5.2008.
[77]Sub-rule (16) omitted by SRO 461(I)/2008, dated 16.5.2008.
[78]Sub-rules (18) TO (24) OMITTED BY THE SRO 461(I)/2008, DATED 16.5.2008.
[79]Subs. By the SRO 662(I)/2005, dated 25.6.2005.
[80]Inserted vide SRO 713(I)/2018 dated 8.06.2018.
[81]Added vide SRO 713(I)/2018 dated 8.06.2018.
[82] Word "drug' Subs. By the SRO 662(I)/2005 dated 25.6.2005.
[83]Substituted for the word "fifty" by SRO 877(I)/2000, dated 9.12.2000

(6) Any fee deposited under sub-rule (3) shall in no case be refunded.

27. Duration of certificate of registration. A certificate of registration under this Chapter, [84][shall] unless earlier suspended or cancelled, be in force for a period of five years from the date of [85][Registration of the drug] and may thereafter be renewed for periods not exceeding five years [86][and a certificate to this effect shall be issued within one month] at a time.

[87][Provided that an application [88][shall be] made within Sixty days after the expiry of the registration and when an application has been made as aforesaid the registration shall subject to the orders passed on the application for the renewal continue in force for the next period of five years:]

[89][Provided further that one time opportunity shall be given to those firms who have not complied with the first proviso since 1st January, 2010 till the issuance of this notification and those within sixty days after issuance of this notification shall be deposit three times of their applicable renewal fee for their registration to continue to be valid until explicit orders are passed on the request of the Registration Board. After the expiry of sixty days of issuance of this notification, the registration of the product shall be considered as cancelled and any manufacturing shall be penalized under the provision of the Act.

Provided also that those firms do not fulfill the first proviso, an additional fee shall be charged equivalent to applicable renewal fee for each month till one year of the expiry of registration and after one year of the registration shall be cancelled.]

[90][Provided further that in case of an imported drug, the renewal may be granted and a renewal certificate shall be issued, if in the opinion of the Registration Board it is necessary to do so in the public interest.]

28. Certificate of registration. A certificate of registration of drug shall be issued in form 6 .

29. Procedure for Registration. (1) The Registration board may, if it considers necessary, [91][in case of a new drug molecule], cause the application for registration and the information and material supplied to it under rule 26 to be evaluated by a Committee on Drugs Evaluation "consisting of experts related to the suspect of the drug to be evaluated and obtain its report.

[92][Provided that in case of a drug product having the same active ingredient or salt thereof, therapeutic use, dosage form and route of administration that has already been approved

[84]Added vide SRO 468(I)/78, dated 6.5.1978.
[85]Substituted, vide SRO 468(I)/78, dated 6.5.1978
[86]Inst. By the SRO 662(I)/2005, dated 25.6.2005
[87]Substituted "proviso" by SRO 691(I)/91, dated 29.7.1991.
[88]Substituted vide SRO 1134(I)/2014 dated 17.07. 2014.
[89] Added vide SRO 1005(I)/2017 dated 18.09.2017.
[90]Proviso subs. By the SRO 662(I)/2005, dated 25.6.2005.
[91]Inserted by the SRO 662(I)/2005, dated 25.6.2005.
[92]Proviso added by the SRO 662(I)/2005, dated 25.6.2005.

by the Ministry of Health which has not been withdrawn from sale, for reasons of safety or effectiveness, the provision of the inspection report conducted within least twelve months, along with the application for registration shall be sufficient for evaluation.]

(2) The Registration Board may, before issuing a [93][certificate of registration], cause the premises in which the manufacture is proposed to be conducted to be inspected by itself or by its sub-committee or by a panel of Inspectors or experts appointed by it for the purpose, which may examine all portions of the premises and the plant and appliances, inspect the process of manufacture intended to be employed and the means to be employed for standardizing, if necessary, and testing the substances to be manufactured and enquire into the professional qualification of the technical staff employed.

(3) Where inspection under sub-rule (2) is carried out by a sub-committee or panel of experts or Inspectors appointed under the said sub-rule, it shall forward to the Registration Board a detailed report of the result of the inspection.

(4) If the Registration Board, after such further enquiry, if any, as it may consider necessary, is satisfied of its safety, action, efficacy, quantity and economical value [94][or where the public interest so requires], it may register the drug and issue a certificate of registration in form 6, subject to such specific conditions as it may specify.

(5) The Registration Board [may], while registering a drug under sub-rule (4), approve the details as supplied by the applicant to approve them with amendments as it may deem fit in respect of the following particulars, namely:--

(a) the name under which the drug may be sold;

(b) the labelling;

(c) the statement of all the representations to be made for the promotion of the drug in respect of –

(i) the claims to be made for the drug;

(ii) the route of administration;

(iii) the dosage;

(iv) the contra-indications, the side effects and pre-causations, if any; and

[(d) Omitted vide S.R.O 551(I)/92, dated 3-7-1993.]

[95][(5-A) where the Registration Board registers a new drug [96][or molecule], it may recommend to the Federal Government for fixation of maximum price of such drug [97][or molecule.]

[93]Substituted for the word licence" by SRO 6(I)/77, dated 31.12.1976.
[94]Inserted the words by SRO 6(I)/77, dated 31.12.1976
[95]Added "sub-rule (5-A) vide S.R.O 551(I)/93, dated 3.7.1993.
[96]Words inst. By the SRO 662(I)/2005, dated 25.6.2005.

(6) The Registration Board shall, before registering a new drug [98][or molecule] for which the research work has been conducted in other countries and its efficacy, safety and quality has been established therein, require the investigation on such pharmaceutical, pharmacological and other aspects, to be conducted and clinical trials to be made as are necessary to establish its quality and, where applicable, the biological availability, and its safety and efficacy to be established under the local conditions:

Provided that under special circumstances to be recorded in writing the Registration Board may register a drug and require such investigations and clinical trials to be conducted after its registration.

(7) A new drug, [99][or molecule with a slight change in chemical formula/salt with the same therapeutic indications as of the already registered molecule] where new method of manufacture is contemplated or a change is proposed in source, standard of specification of the active ingredient or the finished product, may not require full investigations and clinical trials except insofar as they are necessary for the purposes of establishing bio-equivalence absorption, acceptability or other such features.

(8) Where it is necessary in the public interest so to do the Registration Board may register a drug on its own motion without having received o any application for registration.

(9) If the Registration Board is not satisfied as to the safety, efficacy, quality or economic value of a drug [100][or where the public interest so requires] it may, [101][* * *], reject the application for registration and inform the applicant of the reasons for such rejection in writing [102][within a period not exceeding thirty days].

(10) Rejection of an application for the registration of a drug shall not debar an application from submitting a fresh application under rule 25.

30. Conditions of registration of drug. (1) The relevant provisions of the Ordinance and the rules in respect of the registered drug, shall be complied with.

(2) The import, manufacture and sale, of drugs shall be in accordance, with the information in respect of those drugs or in any supplementary information or, where such information was amended by the Registration Board, in accordance with such amended information on the basis of which such drugs were registered:

Provided that deviations from any such information may be made only after obtaining prior approval of the Registration Board.

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[97]Words added by the SRO 662(I)/2005, dated 25.6.2005
[98]Words added by the SRO 662(I)/2005, dated 25.6.2005
[99]Words added by the SRO 662(I)/2005, dated 25.6.2005
[100]Inserted the words by SRO 6(I)/77, dated 31.12.1976
[101]Omitted the words “after providing an opportunity of being heard to the applicant” by SRO 6(I)/77, dated 31.12.1976.
[102]Words by the SRO 662(I)/2005, dated 25.6.2005.

(3) The indications, contra-indications, side effects, the dosage and causations, if any, as have been approved for the purpose of registration of a drug shall be clearly specified in the labelling and promotion.

(4) Every drug shall be produced in sufficient quantity so as to ensure its regular and adequate supply in the market.

(5) The manufacture of any drug shall not, without the prior approval of the Registration board, be discontinued for a period which may result in its shortage:

Provided that in the circumstances beyond the control of manufacture of a drug which may lead to reduction in the production of that drug, the circumstances may be intimated to the Registration Board.

(6) A record of quarterly production and disposal of a drug shall be maintained and disposal of a drug shall be maintained and supplied to the Chairman of the Registration Board in form 7 in the months of January, April, July and October each year.

(7) In case of an imported drug, the indent or any other approved representative in Pakistan of the foreign firm shall ensure regular and adequate supply of the drug in Pakistan.

[103][(7-A) The indenter, importer or manufacturer's authorized agent shall issue a warranty in form 2-A for any drug indented or sold by him for the purpose of re-sale or distribution;]

[104][(7-B, 7-C)]

(8) In respect of new drug records, including adequately organized and indexed files, shall be maintained containing full information regarding:--

(a) animal of clinical investigations and tests conducted by the manufacturer or reported to him by any person concerning that drug:

(b) reports from the scientific literature or the bibliography therefrom that are available to him concerning that drug;

(c) experience, investigations, studies and tests involving the chemical or physical properties or any other properties of that drug;

(d) any substitution of another substance for that drug or any mixing of another substance with that drug;

(e) any error in the labelling of that drug;

(f) any bacteriological or any significant chemical or physical or other change or deterioration in any batch of that drug;

[103]Subs. By the SRO 461(I)/2008, dated 18th May, 2018.
[104]Omitted by the SRO 461(I)/2008, dated 18th May, 2008.

(g) any failure of one or more distributed batches of that drug to meet the required specifications;

(h) any unexpected side effects, injury, toxicity or sensitivity reaction associated with the clinical uses studies, investigations and tests respecting that drug; and

(i) any unusual failure of that drug to produce its expected pharmacological activity.

(9) The following information shall be supplied to the Registration Board—

(a) on request, reports in duplicate of all records respecting the information contemplated by paragraphs (d), (e) and (f) of sub-rule (8); and

(b) immediately upon receipt by him , reports in duplicate of all records respecting the information contemplated by paragraphs (d), (e) and (f) of sub—rule (8); and

(c) as soon as possible and in any event within fifteen working days of their receipt by him report in duplicate of contemplated in paragraphs (g), (h) and (i) of sub-rule (8).

[105][(10) If a drug or any of its ingredients, which is imported or manufactured by a company in Pakistan is also approved for registration and free sale by its subsidiary, sister concern, associate or parent company in the country where it was originally developed or in any of the countries namely, U.S.A. European Union |Countries, Canada, Japan, Australia, and--

(a) if that drug at any time, for safety reasons is withdrawn or banned or certain restrictions are imposed in any of the said countries, then it shall be the responsibility of the manufacturer in Pakistan or as the case may be, the indentors, the immediately withdraw the drug from the market in Pakistan or, as the case may be to impose similar restriction and to inform the Registration Board within fourteen days of such an information having come, to his knowledge and having taken the necessary action. The Registration Board after getting the said intimation shall take similar action for the same drugs available from other sources within shortest possible time;

(b) if clinical information for a drug is approved by the Drug Regulatory Authority in any of the said countries, the same clinical information shall be considered as approved for drug registration in Pakistan unless modified by the Registration Board on the basis of scientific data available to it, and such clinical information may include indications, contra-indications, side effects precautions, dosage, etc;

(c) if an adverse drugs reaction not otherwise included in the application for registration, is registered in any of the said countries, it shall be the responsibility of the concerned manufacturer or in case of imported drugs the indentors of manufacturer agent in Pakistan to be aware of such adverse action and to report to the Registration Board within thirty days of becoming so aware.

(11) the manufacturer or, as the case, may be, the indentor shall follow the ethical criteria for medical drug promotion as given in Schedule G.

[105]Added by SRO 1362(I)/96, dated 28.11.1996.

(12) The Manufacturer or, as the case may be, the indentros shall supply the information in relation to safety, efficacy, production, quality, or availability of the drugs as and when required by the Registration Board with a view to ensure safety; efficacy or quality of the drug; and]

[106][(13) The Application for conducting clinical trials shall be made to the Registration Board addressed to its secretary and shall be accompanied with a five thousand rupees; and]

[107][(14) No vavancies and sera, whether imported and locally manufactured, shall be released for sale, unless a "Lot Release Certificate" is obtained from the Federal Government Analyst, National Control Laboratory for biological.]

Chapter 4

ADVERTISING OF DRUGS, ETC.

31. Conditions of Advertising.[108][(1) The Federal Government may, after seeking advice of the Committee on Advertising, allow the advertisement of a drug, or any substance or a remedy as specified in Schedule D-1 or a treatment or offer of a treatment for any disease, approve the contents of such advertisement and specify conditions subject to which such advertisement shall be made:

Provided that the Federal Government may, if in its opinion the public interest so required, withdraw the approval granted to any advertisement or modify or alter any condition subject to which the advertisement was approved.

[109][(1-A) An application for advertisement of any drug, substance, remedy, treatment or offer of treatment for any disease shall be made it Form-8, addressed to the Secretary of the Commissioner on Advertising and there shall be made a separate application for each advertisement.]

[(1-B) An application under sub-rule (1A) shall be accompanied by the proper fee specified in Schedule F:] and

[110][(1-C) The approval of the advertisement, granted under sub-rule (1), shall be valid for a period for two years only.]

(2) A drug or any substance referred to in clause (ii) of Section 24 may be advertised to the medical, pharmaceutical and allied professions, without referring to the Federal Government, through medical representatives or thorough professional journals and publications which are meant for circulation exclusively amongst the members of the medical, pharmaceutical and allied professions.

Provided that:

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[106]Added by SRO No. 877(I)/2000, dated 9.12.2000.
[107]Added by SRO 779(I)/2001, dated 5.11.2001.
[108]Substituted "sub-sections(2) & (3) vide SRO No. 871(I)/78, dated 8th July, 1978
[109]Inserted sub-rule (1A) by SRO 691(I)/91, dated 29.7.1991.
[110]Added sub-rule (1-C) vide SRO 786(I)/97, dated 5.9.1997

(i) one copy of each issue to such journal or publication is sent to the Drug Administration of the Health Division; and
(ii) the Federal Government may, after giving an opportunity of being heard, prohibit the publication of any advertisement in any such journal if it is found to violate any of the conditions specified under sub-rule (1)].

(3) Advertisements under sub-rule (2) shall be subject to the following conditions, namely:

(i) All claims shall be made in accordance with those approved for registration of that drug.

(ii) Where the usual information on indications and dosage is provided, the advertisement material shall contain information of contra-indications, side effects and other necessary precaution as may be applicable.

(4) A drug [111][or any substance referred to in clause (ii) of Section 24], may be advertised through press without reference to the Federal Government if it is merely intended to inform the public of the availability or the price of such drug [112][or any substance referred to in clause (ii) of Section 24], subject to the condition that Federal Government may prohibit such advertisement if, in its opinion, the public interest so requires.

(5) A drug [113][or any substance referred to in clause (ii) of Section 24], may be advertised to the medical, pharmaceutical and allied professions through a documentary film.

(6) No advertisement under this rule shall contain any direct or indirect comparison in any way with any other drug or substance or remedy for any disease for the purpose of attracting customers or with a view to discredit other such product.

(7) Advertisement material shall be presented with courtesy and good tastes and words and phrases implying urgency, uniqueness or, such expressions which are absolute in character, such as. “The most potent,” “the most rapid”, the most efficacious”, or which make exaggerated claims or too general claims, such as “effective in all cases” or “effective against all complaints” or superlatives shall be avoided.

[114][(8) Advertisement of a drug [115][or any substance referred to in clause (ii) of Section 24], to the public shall include such information on any risks or other precautions as may be necessary for the protection of public health.

(9) No drug or any other substance shall be advertised in a manner which encourages self-medication or use to the extent that it endangers health.

(10) No drug or any remedy, treatment or offer treatment of any disease specified in Schedule E, shall be advertised [116][except as provided in sub-rule (2)].

[111]Added vide SRO No. 871(I)/78, dated 8.7.1978.
[112]Added vide SRO No. 871(I)/78, dated 8.7.1978.
[113]Added vide SRO No. 871(I)/78, dated 8.7.1978.
[114]Substituted “sub-rule(8) vide SRO No. 471(I)/89, dated 25.5.1989.
[115]Added vide SRO No. 871(I)/78 dated 8.7.1978.

(11) Reminder publications for the medical and allied professions shall include name of the drug and its exact compositions, the price, the name and address of the manufacturer and a statement to the effect that "Full information is available on request".

32. Sampling of drugs. Samples of drugs may be provided to the physicians or dentists or pharmacists veterinarians or a medical institution in a reasonable quantity and in reduced packing marked with the words "Physician's Sample Not for Sale".

33. Expenditure on advertisement. No. person shall spend more than five per cent of his turnover on advertisement sampling and other promotional activities in respect of drugs.

[117][Explanation. The expenditure on pay and allowances of the field force connected with the promotional activities shall not be included in expenditure for the purpose of this rule.]

34. Substances required to be prescribed under Section 24. Any substance or a mixture of substances offered for sale which is injurious or likely to become hazardous, to the health of a person shall be deemed to be substance for the purpose of Section 24 of the Ordinance.

[118]**[35. Retailer's discount.** The retailer's discount shall be 15% of the maximum retail price.]

[119]**[36. Prohibition off re-use of disposable medical devices.** The re-use of disposable medical devices shall be prohibited.]

[116]Added vide SRO 471(I)/89, dated 25.5.1989.
[117]Added "explanation" vide SRO 691(I)/91, dated 29.7.1991
[118]Added by SRO No. 1017(I)/86, dated 13.11.1986.
[119]Added by SRO 916(I)/2010, dated 30.9.2010

SCHEDULE A

[See rule 2 (e)]

Form 1

[See rule 5 (1)]

APPLICATION FOR GRANT/RENEWAL OF A LICENCE TO MANUFACTURE BY WAY OF BASIC MANUFACTURE/SEMI-BASIC MANUFACTURE/ FORMULATION/REPACKING

I/We .....of .....hereby apply for the grant of a licence to manufacture by way of.....on premises situated at .....

2. The drug(s) or class(es) of drugs intended to be manufactured :-

(1) Class(es) of drugs.

(2) Dosage form(s) of drugs.

(3) Name of the drug(s).

3. I enclose :-

(i) Particulars regarding the legal status of the applicant (i.e. in case of proprietorship the names) of proprietors and their address (es), in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).

(ii) Details of the premises including layout plan of the factory.

(iii) Details of the section-wise equipment and machinery for manufacture and quality control.

(iv) Names and qualifications of the Production Incharge and Quality Control Incharge for supervising manufacturing processes and Quality Control Department, and other technical staff working in these departments.

4. The premises and plan will be ready for inspection on …….or are ready for inspection.

Date…….. Signed……

Place…… Name Designation and

Address……

PROFORMA
DETAILS OF THE FIRM

Name of the Company .....
Type of ownership (Partnership, Proprietorship, Public limited, Private limited, etc.)

Name(s) of Proprietor(s)/Director(s)/Partner(s).

Date of Establishment.

Initial investment (and details of equity shares).

Present investment (and details of equity shares).

Profit and loss statement as per audited accounts for the last five years:

Year	Investment Turnover	Percentage 1% before tax for Central Research Fund	percentage of Profit	
		Calculated Paid	investment	Turnover

Note: Copies of balance sheets to be enclosed with the application for renewal only"; and

(6) in Schedule B, in paragraph (2), in clause (k), for the semi colon and word"; and" a colon shall be substituted and thereafter the following proviso shall be inserted, namely:

Provided that the conditions of location may be relaxed by the Board in suitable cases for grant or renewal or a licence subject to such conditions as it may deem fit, if the surroundings and the premises, in the opinion of the Board, are satisfactory for the intended manufacture.]

FORM 1-A
[See rule (5(I)]
APPLICATION FORM FOR RENEWAL OF A LICENCE TO MANUFACTURE DURGS BY WAY OF FORMULATION/BASIC MANUFACTURE/SEMI-BA SIC MANUFACTURE/REPACKING

I/We ..... of ..... hereby apply for the renewal of a licence to manufacture by way of on premises situated at .....

2. The drug(s) or class(es)of drugs intended to be continued to be manufactured:-
(i) Class(es) of drugs.
(ii) Dossage form(s) of drugs.
(iii) Name of the drug(s) registered/approved.

3. There have been/have not been any change in respect of
(i) Name of the proprietor/directors/partner(s)

(ii) Details of the premises including layout plan of the factory.
(iii) Details of the section-wise equipment and machinery for manufacture and quality control.
(iv) Names and qualifications of the Production Incharge and Quality Control Incharge for supervision of manufacturing processes and Quality Control Departments, and other technical staff working in these departments

4. Statement of the Central Research Fund.

Following statement, as per audited accounts/based on Income Tax Return for the last five years:-

Year	Investment	Turn-over	CRF due	C R F paid as per Col. 4
1	2	3	4	5

Signed…….

Date

Place

Name, designation and address of the signatory .....

Note:-Strike off which is not applicable.

Attested copies of the last two income tax assessment orders of the Income Tax Department attached.

FORM 2
[See rule 7]
GOVERNMENT OF PAKISTAN
Licence to Manufacture

…….
is/are hereby licensed to manufacture by way of Basic Manufacture/Semi Basic manufacture/Formulation/Repacking at the following premises:-

2. This licence permits the manufacture of.
3. This licence shall, in addition to the conditions specified in the rules made under the Drugs Ordinance/Act, 1976, be subject to the following conditions namely:-

(i) The licence will be in force for a period of two years from the date of issue unless earlier suspended or cancelled.

(ii) The licence authorises the sale by way of wholesale dealing and storage for sale by the licensee of the products manufactured under this licence, subject to the conditions applicable to licences for sale.

*(iii)*Name of the approved expert staff.

.....	.....
.....	.....

Date of issue .....

Secretary, Central Licensing Board.	(Seal)	Chairman, Central Licensing Board.

FORM 2A
(See rules 19 and 30)
Warranty under Section 23(L)(I) of the Drugs Act, 1976

I.....being a person resident in Pakistan, carrying on business at (full address) ..... under the name of.....(and being an importer/indenter/authorised agent of .....), do hereby give this warranty that the drugs here-under described as sold/indented by me/specified and contained in the bill of sale, invoice, bill of lading or other document describing the goods referred to herein do not contravene in any way the provisions of section 23 of the Drugs Act, 1976.

Dated (Signed)

1. Name(s)· of the drug(s): Batch number(s)

(i)

(ii)

2. Description of bill of sale, invoice, bill of lading or other document (if any).

Signed .....

FORM 3
[See rule 21(I)]
APPLICATION FOR LICENCE TO MANUFACTURE DRUG(S) FOR EXPERIMENTAL PURPOSES.

I/We ..... of ..... hereby apply for a licence to manufacture drug(s) specified below for experimental purposes at ..... and I/We undertake to comply with the conditions applicable to the licence under rule 22 of the Drugs (Licensing, Registering and Advertising) Rules, 1976.

Name and quantity of drug(s) to be manufactured for the said purposes:.

Signature.....
Name .....
Address .....
Countersigned by .....

FORM 4
[See rule 21(3)]
LICENCE TO MANUFACTURE DRUG(S)
FOR EXPERIMENTAL PURPOSES

Mr./Messrs ..... of ..... is/are hereby licensed to manufacture the drug(s) specified below for experimental purposes at ..... :. or at such other place(s) at the. Central Licensing Board may from time to time permit.

2. The licence is subject to the conditions prescribed in rule 22 of the Drugs (Licensing, Registering and Advertising) Rules, 1976, and such other conditions as n3ay be subsequently prescribed or Specified by the Central Licensing Board in this behalf.

3. This licence shall unless previously suspended or cancelled be in force for a period of two years from the date specified below:-

Name of drugs with quantity to be manufactured.

Date:..... Licensing Authority.
Place:.....

FORM 5
[See rule 26(I)]
APPLICATION FORM FOR REGISTRATION OF A DRUG FOR LOCAL MANUFACTURE

Having the same active ingredient or salt thereof, therapeutic use, dosage form and route of administration that has already been approved by the Minister of Health, already on sale in local and / or International Market.

I/we.....of .....hereby apply for registration of the drug namely .....details of which are enclosed.

Date ..... Signed ……
Place .....

ENCLOSURE OF THE APPLICATION FOR REGISTRATION OF A DRUG FOR LOCAL MANUFACTURE

Dosage Form:……..

1. Name and address of the manufacturer (applicant):
2. Brand (Proprietary) name of Drug.
3. The chemical name(s) and, as appropriate and available the established (generic) names and synonyms of the drug.
4. Strength of active ingredient(s) per unit, e.g., each tablet or 5ml, etc. contains.
5. Pharmacological group.
6. Recommended clinical use.
7. Proposed route of administration.
8. Proposed dosage.
9. Proposed shelf life of the drug.
10. Proposed storage conditions of finished product.
11. Unit price of the drug, e.g. per tablet, per capsule, per 5ml, etc.
12. In case of international availability, provide the following information, namely:-
    (a) Name of the drug;
    (b) Country where sold / registered; and
    (c) Name of company selling the drug or having registration to manufacture (include supporting documents/ proof of international registration).
13. Brand name(s) of drug available in Pakistan.
14. Name(s) of company (s)manufacturing in Pakistan.
15. Composition (actives & excipients)(including statement of the quantitative composition, giving the weight or measure for each active substance used in the manufacture of the dosage form.
16. Outline of method of manufacture.
17. Persons under whose direct supervision and control the drug is manufactured with the following details, namely:-
    (a) Total number of technical staff; and
    (b) Name, qualification and designation of the persons directly supervising the manufacture of the drug applied for registration, and any change shall be properly documented and record maintained by the manufacturer.
18. Name of equipments that will be used in the manufacture of the drug applied for registration:

	cGMP		Complaint	
1.	_____Yes	☐	No	☐
2.	_____Yes	☐	No	☐
3.	_____Yes	☐	No	☐

4. _____Yes ☐ No ☐

19. Full descriptions of the specifications and analytical methods necessary to assure the identity, strength, quality, purity and homogeneity throughout the shelf life of the drug product.
20. Name, qualification and designation of the persons who will be responsible for the quality control of the drug.
21. Description of the equipment to be used for the quality control of the active raw material and the finished products.
22. Labelling and prescribing information (to be mentioned on the pack/ leaflet) specimen or draft shall be submitted for the following class as of drugs, namely,:--
    (a) C.N.S. stimulants;
    (b) Drugs affecting uterine motility;
    (c) Drugs inhibiting hormonal production;
    (d) Hormones and other steroidal preparation excluding preparations for external and topical use;
    (e) Narcotic drugs as per Single Convention on Narcotic Drugs 1961; and
    (f) Psychotropic substances mentioned as per convention on psychotropic substances, 1971.

    (Specimen of label to be submitted as soon as production starts)
23. Facility of water processing with specifications.
24. Environment control processing with details.
25. Type of container/ packaging.
26. A copy of last Inspection Report conducted by the Ministry of Health.

UNDERTAKING

I/WE hereby undertake that the above given information is true and correct to the best of my /our knowledge and belief.

FORM -5-A
[See rule 26 (1)]
APPLICATION FORM FOR REGISTRATION OF AN IMPORTED DRUG

I/We .....of .....hereby apply for registration of the drug, namely.....details of which are enclosed.

Date .....
Place .....

Signed.....

ENCLOSURES OF THE APPLICATION FOR REGISTRATION OF AN IMPORTED DRUG

1. Name and address of the indentor or agent.
2. Name and address of manufacturer of the drug.
3. Brand (Proprietary) name of the drug.
4. The chemical name(s) and, as appropriate and available, the established (generic) and synonymous of the drug.
5. Strength of active ingredient(s) per unit, e.g., each tablet or 5ml, etc. contains.
6. Country from where the drug is proposed to be imported.
7. The names of the countries, other than Pakistan, wherever the drug is registered and sold. Specify the brand name (s), if other than the brand name applied for.
   (Free sale certificate of country of import to be attached)
8. Pharmacological group.
9. Proposed route of administration.
10. Composition (actives & excipients) including statement of the quantitative composition, giving the weight or measure for each active substance used in the manufacture of the dosage form.
11. Recommended clinical use.
12. Outline of method of manufacture.
13. A full description of the specifications and analytical methods necessary to assure the identity, strength, quality, purity and homogeneity throughout the shelf life of the drug product.
14. Labelling and prescribing information (to be mentioned on the pack/leaflet) specimen or draft shall be submitted.
15. Proposed dosage.
16. Proposed shelf life of the drug.
17. Unit price of the drug, e.g. per tablet, per capsule, per 5ml, etc.
18. Proposed storage conditions of the finished product.
19. Persons under whose direct supervision and control the drug applied for registration shall be manufactured with the following details, namely:-
    a. Total number of technical staff; and
    b. Name, qualification and designation of the persons directly supervising the manufacture of the drug, and any change shall be properly document and recorded and maintained by the manufacturer.
20. Name of equipments that will be used in the manufacture of the applied drug:

	cGMP		Complaint	
1.	_____Yes	☐	No	☐
2.	_____Yes	☐	No	☐
3.	_____Yes	☐	No	☐
4.	_____Yes	☐	No	☐

21. Production capacity of the manufacturer per shift for the drug applied.

22. Name, qualification designation of the persons who will be responsible for the quality control of the drug.
23. Description of the equipment to be used for the quality control of the active raw material and the finished products.
24. Facility of the water processing, with specification.
25. Environment control processing with details.
26. Attach the last Inspection Report conducted by the concerned Regulatory Authorities.
27. Clinical data (along with data of clinical trials conducted and safety data of the drug, with reported side effects and adverse drug reactions in the indigenous community).
28. Clinical justification.
29. Dosage form stability profile.
30. Any other relevant information that may be required by the Board.

UNDERTAKING

I/We hereby undertake that the above given information is true and correct to the best of my / our knowledge and belief.

Signature of the authorized importer.

FORM-5B
[See rule 26(3A)]
APPLICATION FORM FOR RENEWAL OF REGISTRATION OF ALL KINDS OF DRUGS

I/We ..... of ..... hereby apply for renewal of registration of the drug, namely .....details of which are as follows.

Date ……. Signed……

Place…….

ENCLOSURES OF THE APPLICATION FOR RENEWAL OF REGISTRATION OF A DRUG

Dosage Form:……

1. Brand (Proprietary) name of the drug.
2. Strength of active ingredient(s) per unit, e.g., each tablet or 5ml, etc. contains.
3. Name and address of the manufacturer.
4. Name and address of the agent or indentor in case of imported drug.
5. Whether the drug is registered for local manufacture or import.
6. Patent number in Pakistan & its expiry date.
7. Name of the registered drug with its registration number and date of initial registration and last renewal.
8. Changes, if any, in information furnished at the time of initial registration or last renewal.
9. If withdrawn from the market anywhere:

(i) The name of the country; and
(ii) The reasons thereof.

Undertaking

We hereby give this undertaking that the above mentioned information is true and correct to the best of our knowledge.

…… ……..
Production Manager Quality Control Manager."

FORM-5C
[See Rule 26(1)]

TO WHOM IT MAY CONCERN CERTIFICATE OF DRUGS REGISTERED UNDER THE DRUGS ACT, 1976

Name and dosage form of product .....
Name and amount of each active ingredient .....

Manufacturer and or when applicable the person responsible for Placing the Product on the market ..... Address(es).....

It is certified :

- This product has been authorised to be place of the market for use in this country.
- Number of Registration and date of issue if plicable.
- This product has not been authorised to be placed on the market for use in this country for the following reason-

.....
.....
.....

It is also certified that (a) the manufacturing plant in which the product is produced is subject in inspections at suitable intervals, and (b) the manufacturer conforms to requirements for good practices in the manufacture and quality control, in respect of products to be sold or distributed within the country of origin or to be exported.

(Signature of designated authority (Place and date)

FORM 5-D
[See Rule 26(1)]

APPLICATION FORM FOR REGISTRATION OF A DOSAGE FORM CONTAINING A NEW DRUG MOLECULE OR A NEW COMBINATION/ DOSAGE FORM, FOR LOCAL MANUFACTURE

I/We……..of ……. Hereby apply for registration of the drug, namely…….. details of which are enclosed.

Date…….. Signed……
Place…….

ENCLOSURES OF THE APPLICATION FOR REGISTRATION OR A NEW DRUG OF A NEW COMBINATION/ DOSAGE FORM

Dosage Form…….

1. Name and address of the manufacturer.
2. Bran (Proprietary) name of the drug.
3. The chemical name(s) and, as appropriate and available, the established (generic) and synonyms of the drug.
4. Strength of active ingredient(s) per unit, e.g. each tablet or 5ml, etc. contains.
5. Pharmacological group.
6. Proposed route of administration.
7. Composition (actives & excipients) including statement of the quantitative composition, giving the weight or measure for each active substance used in the manufacture of the dosage form.
8. Outline of method of manufacture.
9. Recommended clinical use.
10. Full description of the specifications and analytical methods necessary to assure the identity, strength, quality, purity and homogeneity throughout the shelf life of the drug product.
11. Labelling and prescribing information (to be mentioned on the pack/leaflet) specimen or draft shall be submitted.
12. Proposed dosage.
13. Proposed shelf life of the drug.
14. Unit price of the drug, e.g. per tablet, per capsule, per 5ml, etc.
15. Proposed storage conditions of finished product.
16. Persons under whose direct supervision and control the drug applied for registration shall be manufactured with the following details, namely:--
    a. Total number of technical staff; and
    b. Name, qualification and designation of the persons directly supervising the manufacture of the drug applied for registration, and any change shall be properly documented and record maintained by the manufacture.
17. Name of equipment that will be used in the manufacture of the applied drug:

	cGMP		Complaint	
1.	_____Yes	☐	No	☐
2.	_____Yes	☐	No	☐
3.	_____Yes	☐	No	☐

4. _____Yes ☐ No ☐

18. Name, qualification and designation of the person who will be responsible for the quality control of the drug.
19. Description of the equipment, to be used for the quality control of the active raw material and the finished products.
20. Facility of the water processing with specifications.
21. Environment control processing with details.
22. Attach the last Inspection Report conducted by the Ministry of Health.
23. Clinical data l(along with data of clinical trials conducted and safety data of the drug, with reported side effects and adverse drug reactions in the indigenous community).
24. Clinical justification.
25. Dosage form stability profile.
26. Any other relevant information that may be required by the Board.

Undertaking

I/We hereby give this undertaking that the above mentioned information is true and correct to the best of mu/our knowledge and belief.

…… ……..
Production Manager Quality Control Manager."

FORM 5-E
[See Rule 26(1)]

APPLICATION FORM FOR THE REGISTRATION TO MANUFACTURE A PATENTED DRUGS

I/We …….. of …….. hereby apply for registration of the drug, namely ……. Datails of which are enclosed.

Date …… Signed……..
Place…….

ENCLOSURES OF THE APPLICATION FOR REGISTRATION OF A PATENTED DRUG

Dosage Form……..

1. Name and address of the manufacturer (applicant).
2. Name of the drug.

3. Chemical name(s) and, as appropriate and available, the established (generic) and synonymous, Chemical Abstracts Service (CAS) registry number and code number.
4. Structural formula: Provide the chemical structure (including stereochemistry, where applicable), molecular formula, and molecular weight.
5. Physical and chemical characteristics: Describe physiochemical characteristics including, where applicable, such information and description regarding solid-stage form, solubility profile melting point, pH, specific rotation, refractive index, etc.
6. Elucidation of structure: Supply physical and chemical data collected to elucidate and confirm the chemical structure of the drug substance.
7. Stability: Describe fully the studies on the stability of the new drug substance and include the results. Reference to stability, information from prior studies or from the literature may be used to meet some or all of these requirements. Also, include information showing the stability, indicating analytical methods used therein.
8. Manufacturer(s) Provide the name and address of each facility, besides the applicant, that participates in manufacturing the drug substance (e.g., performs the synthesis, isolation, purification, testing, packaging or labelling). Describe the operation(s) that each will perform.
9. Method(s) : Of Manufacture and Packaging. Provide a full description of the materials and method(s) used in the synthesis, isolation and purification of the drug substance. This description should include a list of starting materials, reagents, solvents, and auxiliary materials with specifications or a statement of the quality of each. The description should include a diagrammatic flow chart of the synthesis and a detailed description of each step. Any alternate methods or variations in the synthesis should be included with an explanation of the circumstances under which they would be used. If the drug substance is prepared by fermentation or by extraction from natural sources (plant or animal), provide a full description of the process.
10. Strength of active ingredient(s) per unit, e.g. each tablet or 5ml, etc. contains.
11. Pharmacological group.
12. In case of International availability, provide the following information, namely:-
    (a) Name of the drug;
    (b) Country where sold / registered ; and
    (c) Name of company selling the drug or having registration to manufacture (including supporting documents).
15. Proposed route of administration.
16. Composition (actives and excipients) including statement of the quantitative composition, giving the weight or measure for each active substance used in the manufacture of the dosage form.
17. Detailed method of manufacture and packaging.
18. Name of equipments that will be used in the manufacture of the applied drug.

	cGMP		Complaint	
1.	_____Yes	☐	No	☐
2.	_____Yes	☐	No	☐
3.	_____Yes	☐	No	☐

4. _____Yes ☐ No ☐

19. Persons under whose direct supervision and control the applied drug shall be manufactured with the following details, namely:-
    a. Total number of technical staff; and
    b. Name, qualification and designation of the persons directly supervising the manufacture of the drug applied for registration and any change shall be properly documented and record maintained by the manufacture.
20. Name, qualification and designation of the persons who will be responsible for the quality control of the drug.
21. Description of the equipment to be used for the quality control of the active raw material and the finished products.
22. A full description of the specifications and analytical methods necessary to assure the identity, strength, quality, purity and homogeneity throughout the shelf life of the drug product.
23. Labelling and prescribing information (to be mentioned on the pack/ leaflet) specimen or draft shall be submitted.
24. Paten number and country where the first patent was applied for and granted (attach a certified copy of the Letter of Patent).
25. Patent number and date of grant of Patent in Pakistan (attach a certified copy of the Letter of Patent).
26. Expiry date of Patent in Pakistan.
27. Proposed shelf life of the drug.
28. Complete batch formula.
29. Proposed dosage.
30. Attach the last Inspection Report conducted by the Ministry of Health.
31. Clinical data (along with data of clinical trials conducted and safety data of the drug, with reported side effects and adverse drug reactions in the indigenous community).
32. Clinical justification.
33. Dosage form stability profile.
34. Any other relevant information that may be required by the Board.

UNDERTAKING

I/We hereby undertake that the above given information is true and correct to the best of my/our knowledge and belief.

---------- ----------

Production Manager Quality Control Manager."

FORM 6
[See rules 28 and 29(4)]

CERTIFICATE OF REGISTRATION

Certified that following drug(s) are hereby registered under the Drugs Ordinance/Act, 1976:-

Name of Drug(s).
Name of Manufacturer.
Name of Indenter/Manufacturer's agent/Importer (in case of imported drugs only).

2. This registration shall be valid for a period of five years unless earlier suspended or cancelled.

3. This registration is subject to the conditions specified in the Drugs Ordinance/Act, 1976, and .the rules thereunder and to the conditions specified in the enclosure.

Date of Registration …….

Secretary (Seal) Chairman

Registration Board Registration Board

FORM 7
[See rule 30(6)]

STATEMENT SHOWING QUARTERLY PRODUCTION TO BE SUBMITTED IN DUPLICATE

Name of drug. _____

Pharmacological group _____

Name of the Firm. _____

Address. _____

For the quarter ending. _____

Pack size.	No. of Pack	Total quantity in terms of individual units e.g., total No. of tablets, injections tubes litres etc.

1	2	3	
VALUE (in Rs.)		Details of Disposal	
On trade price	On retail price	Indicate whether supplied through normal distribution, channels or exported or supplied to any specific institution.	Value of raw materials used (Active & inactive) (in Rs.)
4	5	6	7

Total.

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SECTION-I
PREMISES

1. **Location and Surroundings**

1.1 Location: The premises shall be located preferably in an industrial area and in any case not in any [120][****] residential or commercial area.

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

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

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

3. Building design and construction (General)

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

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

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

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

(i) floors, walls, and ceilings permit easy cleaning, brick, cement blocks, and other porous materials are sealed;
(ii) floors, walls, ceilings, and other surfaces are hard, smooth, and free of sharp corners where extraneous material can collect;
(iii) joints are sealed between walls, ceilings and floors;

[120]Word "congested" omitted by S.R.O 270(I)/2000, dated 10.5.2000

(iv) pipes, light fittings, ventilation points and other services do not create surfaces that cannot be cleaned; and
(v) screened and trapped floor drains are provided if required.

4. Storage areas

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

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

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

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

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

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

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

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

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

5. Production Department

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

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

5.2. Dedicated facilities for production

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

5.3 General requirement for production areas

(i) *Layout:* the production area shall preferably be laid out in such a way as to allow the production to take place in are &s connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
(ii) *Adequacy:* The adequacy of the working and in-process storage space shall permit the orderly and logical placement of equipment and materials so as to

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

(iii) *Surfaces:* Starting and primary packaging; materials and intermediate or bulk products are exposed to the environment, interior surfaces (wells, floors* and ceilings) shall be smooth and free from cracks and open joints shall not shed particulate matter, and shall permit easy and effective clearing and, if necessary, disinfection.

(iv) *Services:*Pipework, light fittings, ventilation points and other services shall be designed and sided to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they shall be accessible from outside the manufacturing areas.

(v) *Drains:* Drains shall be of adequate size and equipped to prevent backflow. Open channels shall be avoided.

(vi) *Environmental Controls:* Production areas shall be effectively ventilated, with air-control facilities (including control of temperature and, where necessary, humidity and filtration) appropriate to the products handled to the operations undertaken, and to the external environment. These areas shall be regularly monitored during production and non-production periods to ensure compliance with their design specifications.

(vii) *Packaging:* Area(s) for the packaging of pharmaceutical products shall b specifically designed and laid out so as to avoid mix-ups or cross-contamination.

(viii) *Light:* Production areas shall be well lit, particularly where visual online controls are carried out.

6. Ancillary areas

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

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

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

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

SECTION-2

EQUIPMENT FOR PRODUCTION

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

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

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

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

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

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

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

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

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

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

SECTION-3

QUALITY CONTROL DEPARTMENT

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

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

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

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

3.4 Facilities: The quality control laboratory shall have:

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

SECTION-4

DOCUMENTATION

4.1 General the documents shall:

(i) Be designed and prepared, complying with the relevant parts of the drug registration approvals;

(ii) Be approved, signed, and dated by appropriate authorized persons and shall not be changed without authorization;

(iii) Have unambiguous contents and shall clearly state the title, nature, and purpose, and they shall be laid out in an orderly fashion and be easy to check, reproduced documents shall clear and legible.

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

(i) Reference Bodies: Pharmacopoeias, reference standards, reference spectra, and other reference materials, where necessary;

(ii) Testing Procedures: Validated testing procedures in the context of available facilities and equipment;

(iii) Specifications: Appropriately authorized and dated specifications, including tests on identity, content, purity, and quality, for starting and packaging materials and finished products; and where appropriate, for intermediate or bulk products. Specifications for water, solvents, and reagents (e.g., acids and gases) used in production shall also be included.

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

(i) The designated name (if applicable, the International Non-proprietary Name) and internal code reference;

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

(iii) Qualitative and quantitative requirements with acceptance limits; and

(iv) Packaging material shall conform to specifications, with emphasis placed on the compatibility of the material with the drug product it contains.

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

(i) the designated name of the product and the code reference where applicable;

(ii) the designated name (s) of the active ingredient (s) if applicable, the International Non-proprietary Name);

(iii) the label claim or the reference to the formula;

(iv) a description of the dosage form;

(v) direction for sampling and testing or a reference to procedures;

(vi) the qualitative and quantitative requirements with acceptance limits;

(vii) the storage conditions and precautions where applicable; and

(viii) the shelf-life.

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

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

4.6. Packaging instruction: Formally authorized packaging instructions shall exist for each product, pack size, and type which shall normally include or made reference to:--

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

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

(i) the receipt of each delivery of starting material and primary and printed packaging material;

(ii) the internal labelling, quarantine, and storage of starting materials, packaging materials, and other materials as appropriate;

(iii) each instrument and piece of equipment. These shall be placed in close proximity to the equipment;

(iv) sampling, which specify the person (s) authorized to take samples, and the sampling instructions shall include:--

(a) the method of sampling and the sampling plan;
(b) the equipment to be used;
(c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
(d) the amount of sample to be taken;;
(e) instructions for any required sub-division of the samples;
(f) the type of sample container to be used, and whether they are for aseptic sampling or for normal sampling; and
(g) any specific precautions to be observed, especially in regard to the sampling of sterile or naxious material;

(v) Describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk, or finished product is identified with a specific batch number;

(vi) For batch numbering that are applied to the processing stage and to the respective packaging stage shall be related to each other;

(vii) For batch numbering shall assure that the same batch numbers will not be repeatedly used; this applies also to reprocessing.

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

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

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

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

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

4.11. Labels.

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

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

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

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

4.12. Batch Processing Records.

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

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

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

(a) the name of the drug;
(b) the number of the batch being manufactured;
(c) dates and times of commencement, of significant intermediate stages and of completion of production;
(d) initials of the operator of different significant steps of production and, wrjere appropriate, of the person who checked each of these operations (e.g., weighing);
(e) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any

recovered or reprocessed material added);

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

(g) a record of the in-process controls and the initials of the persons(s) carrying them out, and the results obtained;

(h) the amount of drug obtained at different stages of manufacture (yield) explaining any significant deviations from the expected yield;

(i) notes on special problems including details, with signed authorization, for any deviation from the Master Formula.

SECTION-5

SANITATION AND HYGIENE

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

(i) cleaning requirements applicable to all production areas of the plant, with emphasis on manufacturing areas that require special attention;

(ii) cleaning requirements applicable to processing equipment;

(iii) cleaning intervals;

(iv) cleaning materials, their concentration, and the equipment to be used;

(v) responsibilities of outside contractors, if any;

(vi) disposal procedures for waste material and debris;

(vii) pest control measures;

(viii) precautions required to prevent contamination of a drug when rodenticides, insecticides, and fumigation agents are used;

(ix) microbial and environmental monitoring procedures and limits in areas where susceptible products are manufactured; and

(x) the personnel responsible for carrying out cleaning procedures.

5.2. Hygiene

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

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

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

(i) pre-employment medical examination;

(ii) assessment of an employee's health prior to return to his place of employment following illness involving a communicable disease;

(iii) action to be taken in the event of a positive diagnosis or a case suspected of being hazardous to consumers of the products; and
(iv) Routine supervisory check system of employees.

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

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

SCHEDULE B-1

[See rule 16(6)(b)]

REQUIREMENTS OF PLANT AND EQUIPMENT

(A) The Following equipment is required for the manufacture of drugs for external appliances or suspense:--
(1) Mixing tanks where applicable.
(2) Katties, steam, gas or electrically heated.
(3) A suitable power driven mixer.
(4) Storage tanks or pots.
(5) A colloid mill or a suitable emulsifier or homogeniser, where applicable.
(6) A trip-roller mill or an ointment mill, where applicable.
(7) Liquid filling equipment.
(8) Jar or tube filling equipment, where applicable.
Area of minimum of 200 square feet is required for the basic installation.

(B) The following equipment is required for manufacture of Syrups, Exlixirs and Solution:--
(1) Mixing and storage tanks.
(2) Mixer.
(3) Filter press or other suitable filtering equipment such as metal filter or sparkled filter or Also –pad filter.
(4) Water still or Deinoniser.
(5) Various liquid measures and weighing scale.
An area of maximum 300 square feet is required for the basic installations.

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

1 Granulating Section;

2 Tableting Section;

3 Coating Section.

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

1. **Granulating Section.** (1) Disntegrator, where applicable.

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

(3) Granulator.

(4) Oven thermostatically controlled.

2. Tableting Section:--

(1) Tablet machine, single punch or rotary.

(2) Pill machine, where applicable.

(3) Punch and dyes storages cabinet.

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

3. Coating Section:--

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

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

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

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

(D) The following equipment is required for the manufacture of powders:-
(1) Disintegrator, where applicable.
(2) Mixer

(3) Sifter or sieve.
(4) Stainless steel vessels and scoops of suitable material.
(5) Filling equipment.

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

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

(E) The following equipment is required for filing of Hard Gelatin Capsules:--
(1) Mixing and blending equipment.

(2) Capsules filling units.

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

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

(1) Rolling machine.

(2) Trimming machine.

(3) Cutting equipment.

(4) Folding and pressing machine for gauze.

(5) Mixing tanks for processing medicated dressings.

(6) Hot air drying ovens.

(7) Steam sterilizer or dry heat sterilizer.

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

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

(1) Hot air oven electricity heated with thermostatic control.

(2) Kettle, gas or electrically heated with suitable mixing arrangement.

(3) Colloid mill or homegeniser.

(4) Tube filling equipment.

(5) Mixing and storage tanks of stainless steel or of other suitable materials.

(6) Sintered glass funnel, seitz filter or filter candle.

(7) Liquid filling equipment.

(8) Autoclave.

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

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

(1) Mixing and pouring equipment.

(2) Moulding equipment.

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

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

(1) Mixer.

(2) Granulator.

(3) Drier.

(4) Compressing machine.

(5) Pessary and tablet counter.

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

(1) Mixing equipment.
(2) Graduated delivery equipment for measurement of the medicament.
(3) Sealing equipment.
An area of minimum of 200 square feet is required for basic installations.
(J) The following equipment is required for the repacking installations of drugs and Pharmaceutical Chemicals:--
(1) Sifter.
(2) Stainless steel scops and vessels.
(3) Weighing and measuring equipment.
(4) Filling equipment.
An area of minimum of 300 square feet is required for basic packing operations. In the case of operations invoking floating particles of fine powder or dust, a suitable exhaust system should be provided.

(K) Requirements for the manufacture of parenteral preparations:-- The whole

process of the manufacture of parenteral preparations may be divided into the following separate operations:--

(a) **Preparation of the container.**—This includes, cutting, washing, drying sterilization of ampoules or vials prior to filling.

(b) **Preparation of solution.--** This includes preparation and filtration of solution.

(c) **Filling and sealing.--**This includes filling and sealing of ampoules or filling and capping of vials.

(d)Sterilization.

(e) Testing.

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

(1) Strict sanitation shall be maintained throughout the entire plant in order to prevent contamination and to keep out pyrogens. Masks and overalls shall be worn wherever necessary.

(2) The preparation room where the solutions are prepared shall be of such a nature that may be kept scrupulously clean. This room shall be air-conditioned.

(3) The filling and sealing rooms shall likewise be air-conditioned under positive pressure with air locks provided to prevent the entry of air from outside. The walls and floors shall be such as may permit their being sprayed and washed with an antiseptic solution. The benches shall preferably have stainless steel or laminated plastic tops capable of being washed.

(4) In the room provided for aseptic filling and sealing, necessary measures for maintaining sterility and to preventing contamination shall be adopted.

(5) A separate room shall be provided for sterilization, testing (for leaks and floating particles) and drying.

(6) finished products shall be stored in a suitable separate place.

The following equipment required:

Manufacturing Area:--

(1) Storage equipment for ampoules and vials.

(2) Ampoule washing and drying equipment.

(3) Dust proof storage cabinets.

(4) Water still.

(5) Mixing and preparation tanks or other containers. The tanks or containers shall be made of either glass or such material which will not react with the liquid.

(6) Filtering equipments such as filter pass or sintered glass funnel.

(7) Autoclave.

(8) Hot Air Steriliser.

Filling and sealing room:--

(9) Benches for filling and sealing.

(10) Filling and sealing unit.

Aseptic filling and sealing room:--

(11) Bacteriological filters such as seitz filter, candles or sintered glass filters.

(12) Filling sealing unit.

General Room:--

(13) Inspection table with draft and light background.

(14) Leak testing equipment.

(15) Labelling and packing benches.

(16) Storage equipment including cold storage and refrigerators, if necessary.

Note I. The above requirements of this Schedule are subject to modifications at the

discretion of the Central Licensing board if it is of the opinion that having regard to the nature and extent of the manufacturing operations it is necessary to relax or alter in the circumstances of a particular case:

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

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

[121][(L) Requirements for the manufacture of medical devices:

1. Hypodermic Disposable Syringes:

(i) Components Molding:

(a) Plastic Injection Molding Machine.
(b) Barrel Mold.
(c) Plunger Mold.
(d) Gasket Mold.

(ii) Barrel Printing:

(a) Printing Machine
(b) Printing Graviour Roller and Screen.

(iii) Assembling:

Assembling Machine.

(iv) Packaging:

(a) Blister Packing Machine.
(b) Printing Machine.

(v) Manufacturing Area:

Minimum area required for molding, barrel printing, and assembling shall be 900 sq.ft.

2. Hypodermic Disposable Needless:

(i) Components Molding:

(a) Plastic Injection Molding machine.

(b) Hub Mold.

(c) Cap Mold.

[121]Clause (L) added by SRO 916(I)/2010, dated 30.09.2010

(ii) Assembling:

(a) Needle Assembly Machine.
(b) Jigs.

(iii) Manufacturing Area:

Minimum area required for molding and assembling shall be 600 sq.ft.

3. Infusion giving Set:

(i) Components Molding:

(a) Plastic Injection Molding Machine.

(b) Snike Mold.

(c)Spike Cover Mold.

(d) Drip Chamber Mold.

(e) Connector Mold.

(f) Slider Mold.

(g) Roller Mold.

(ii) Tube Extrusion:

Tube Extruder.

(iii) Assebbling:

Chamber Spike Assembly Press.

(iv) Packing/ Sealing:

(a) Poly Sealer.
(b) Blister Packing Machine if required.

(v) Manufacturing Area:

Minimum area required for molding, extrusion, assembling and packing shall be 900 sq.ft.

4. IV Canula / Catheter:

(i) Components Molding:

(a) Plastic Injection Molding Machine.

(b) Wing Mold.

(c) Cap Mold.

(d) Injection Port Mold.

(e) Scap Mold.

(ii) Assembling:

(a) Tube cutting machine.
(b) Forming machine.
(c) Sus pin insert machine.
(d) Silicon tube insert machine.
(e) Oven for epoxy curing.
(f) Silicon coating.

(iii) Packing / Sealing:

Blister Packing Machine.

(iv) Manufacturing Area:

Minimum area required for molding, assembling and packing shall be 200 sq.ft.

5. Sterilization:

(i) Equipment:

(a) Sterilizer.

(b) Cylinders where required.

(ii) Manufacturing Area:

Minimum area required per unit of sterilizer shall be 400 sq.ft.

6. Utilities and Auxiliary Equipment:
(a) Cooling Tower and/ or Water Chiller.
(b) Crusher.
(c) Air Compressor.]

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[122][SCHEDULE B1-A

[see rule 16 (bb) -7]

CONDITIONS OF FACTORY PREMISES

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

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

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

[122]Sch. BI-A added by the SRO 268(I)/83, dated 20th March, 1983.

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

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

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

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

Staff must not be allowed to go home wearing the same clothing they wore at work; emergency showers and eye washing facilities must be provided in the premises. Safety instructions should be strategically displayed in local language. All emergency and safety equipment must be frequently and regular4ly checked and maintained to ensure its conditions satisfactory.

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

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

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

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

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

SCHEDULE B-II

GOOD MANUFACTURING PRACTICES (GMPs) FOR LICENCE TO MANUFACTURE BY WAY OF FORMULATION

Part-1

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SCHEDULE B-II

GOOD MANUFACTURING PRACTICES (GMPs) FOR LICENCE TO MANUFACTURE BY WAY OF FORMULATION

PART-I
GENERAL CONDITIONS
SECTION-I

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

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

SECTION-2

2. Quality assurance system

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

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

SECTION-3

3. Quality Control

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

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

(a) during the period of validity of licence, adequate facilities, trained personnel and approved procedures are available for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for good manufacturing practices purposes.
(b) samples of starting materials, packaging materials, intermediate products, bulk products and finished products are taken by methods and personnel approved of by the quality control department;
(c) test methods are validated;
(d) records are made manually and or by recording instruments demonstrating that all the

required sampling, inspecting, and testing procedures have actually been carried out and that any deviation has been fully recorded and investigated;

(e) the finished products contain ingredients complying with the qualitative and quantitative composition of the products described in the marketing authorization, the ingredients shall be of the required purity, in their proper container, and correctly labelled;

(f) records are made of the results of inspecting and testing materials and intermediate, bulk, and finished products against specifications and product assessment includes a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;

(g) no batch of product is released for sale prior to certification by the authorised persons(s) that it is in accordance with the requirements of the rules;

(h) sufficient samples of starting materials and products are retained to permit future examination of the product if necessary and the retained product is kept in its final pack unless the pack is exceptionally large; and

(i) all quality control procedures are established, validated and implemented; the reference standards for substances are evaluated, maintained, and stored; correct labelling of containers of materials and products is ensured; the stability of the active pharmaceutical ingredients and products is monitored; complaints related to the quality of the product are investigated and environmental monitoring is conducted. All these operations shall be carried out in accordance with written procedures and where necessary, recorded, provided that the Central Licensing Board may allow other arrangements if it is considered necessary for an effective quality control system of the licensee.

3.3 Control Procedures:

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

3.3.2 Sampling: The samples shall: --

(a) be representative of the batches of material from which they are taken and in accordance with the approved written procedure;

(b) be taken in a manner so as to avoid contamination or other adverse effects on quality, and the containers that have been sampled shall be marked accordingly and carefully resealed after sampling;

(c) be taken with care to guard against contamination or mix-up of or by the material being sampled, all sampling equipment that comes into contact with the material shall be clean, and some particularly hazardous or potent materials may require special precautions;

(d) be taken with equipment which shall be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment; and

(e) bear a label indicating: --

(i) the name of the sampled material;

(ii) the batch or lot number;

(iii) identify the container from which the sample has been taken;

(iv) the signature of the person who has taken the sample; and
(v) the date of sampling.

3.3.3 Test requirement for starting and packaging materials:

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

3.3.4 Test requirement for in-process control:

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

3.3.5 Test requirements for furnished products:

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

3.3.6 Production record and batch review:

(i) *Review of Records:* Production and control records shall be reviewed and any divergence or failure of a batch to meet its specifications shall be thoroughly investigated, the investigation shall, if necessary, extend, to other batches of the same product and extend, to other batches of the same product and other products that may have been associated with the specific failure or discrepancy, and a written record of the investigation shall be made and shall include the conclusion and details of follow-up action.
(ii) *Retention of Samples:* Retention samples from each batch of finished product shall be kept for at least one year after the expiry date. Finished products shall usually be kept in their final packaging and stored under the recommended conditions. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials shall be retained for five years. Other starting materials (other than solvents, gases, and water) shall be retained for a minimum of two years if their stability allows; Retention samples

of materials and products shall be of a size sufficient to permit at least two full re-examinations.

3.3.7 Stability studies:

(i) The quality control department shall:--

(a) evaluate the quality and stability of finished pharmaceutical products and, of starting materials and intermediate products; and

(b) establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

(ii) A written programme for ongoing stability determination shall be developed and implemented to include elements such as: --

(a) a complete description of the drug involved in the study;

(b) the complete testing parameters and methods describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;

(c) provision for the inclusion of a sufficient number of batches;

(d) the testing schedule for each drug;

(e) provision for special storage conditions;

(f) provision for adequate sample retention; and

(g) a summary of all the data generated, including the evaluation and the conclusions of the study.

(iii) Stability of the finished product shall be evaluated anddocumented prior to marketing and following any significant changes in the processes, equipment, primary packaging materials, etc.

3.4. Self-inspection:

3.4.1. *General:* The licensee shall conduct repeated self-inspection with a view to evaluate its own compliance with good manufacturing practices in all aspects of production and quality control. The self-inspection programme shall be designed to detect any shortcomings in the implementation of good manufacturing practices and to recommend the necessary corrective actions; Self-inspections shall be performed routinely, and may be, in addition, performed on special occasions, e.g., in the case of product recalls or repeated rejections or when an inspection by the Central Licensing Board is required. The team responsible for self-inspection shall consist of personnel who can evaluate the implementation of good manufacturing practices objectively; all recommendations for corrective action shall be implemented. The procedure for self-inspection shall be documented, and there shall be an effective follow-up programme.

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

(a) personnel;

(b) premises including personnel facilities;

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

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

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

3.4.5. *Self-inspection report: A report shall be made at the completion of self-inspection which shall include: --*
(a) Self-inspection results;
(b) Evaluation and conclusions; and
(c) Recommended corrective actions.

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

3.5. Quality audit

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

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

3.6. Complaints:

3.6.1. *Review of complaints:* All complaints and other information concerning potentially defective products must be carefully reviewed according to written procedures.

3.6.2. *Person authorized:* A person responsible for handling the complaints and deciding the measures to be taken shall be designated, together with sufficient supporting staff to assist him and if this person is different from the authorized person, the latter shall be made aware of any complaint, investigation, or recall.

3.6.3. *Written procedures:* There shall be written procedures describing the action to be

taken including the need to consider, a recall, in the case of a complaint concerning a possible product defect.

3.6.4. *Recording defects and investigation:* Any complaint concerning a product defect shall be recorded with all the original details and thoroughly investigated. The person responsible for quality control shall normally be involved in the study of such problems.

3.6.5. *Investigation:* If a product defect is discovered or suspected in a batch, consideration shall be given to whether other batches shall be checked in order to determine whether they are also affected, in particular, other batches that may contain reprocessed product from the defective batch shall be investigated.

3.6.6. *Follow*-up action: Where necessary, appropriate follow-up action, possibly including product recall, shall be taken after investigation and evaluation of the complaint.

3.6.7. *Recording measures:* All the decisions and measures taken as a result of complaint shall be recorded and referenced to the corresponding batch records.

3.6.8. *Review for recurring problems:* Complaint record shall be regularly reviewed for any indication of specific or recurring problems that require attention.

3.7. Product recalls:

3.7.1. *System:* There shall be a system to promptly and effectively recall from the market the products known or suspected to be defective.

3.7.2. *Authorized person:* A person responsible for the execution and coordination of recalls shall be designated, as well as sufficient staff to handle shall aspects of the recalls with the appropriate degree of urgency, this person shall normally be independent of the sales and marketing organization; if this person is different from the authorized person, the latter shall be made aware of any recall operation.

3.7.3. *Written procedure:* There shall be established written procedures, regularly checked and updated for the organization of any recall activity. Recall operations shall be capable of being initiated promptly at least down to the level of the health institutions and all sale channels including whole sale and where possible retail sale and public notice if required.

3.7.4. *Recall with promptness:* All competent authorities to whom a given product may have been distributed shall be promptly informed of any intention to recall the product because it is, or was suspected of being, defective.

3.7.5. *Distribution records:* The distribution records shall be readily available to the person(s) responsible for recalls, and they shall contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received “samples for clinical tests and medical samples) to permit an effective recall.

3.7.6. *Recording of progress:* The progress of the recall process shall, be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the products.

3.7.7. *Evaluation:* The effectiveness of the arrangements for recalls shall be evaluated from time to time.

3.7.8. *Storage of recalled drugs:* An instruction shall be included to store recalled products in a secure segregated area while their fate is decided.

3.7.9. All concerned to be informed: The Central Licensing and Registration Boards

and other concerned Government authorities shall be immediately informed if it is intended to recall product(s) or if a product has been recalled. Effective system shall be maintained to inform the doctors, pharmacist and public of the recalled products.

Section – 4

4. Personnel

4.1. General: The licensee shall provide: -

(a) Sufficient qualified personnel to fulfil all its responsibilities required under these rules; and

(b) Organization chart.

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

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

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

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

(a) the authorization of written procedures and other documents, including amendments;

(b) the monitoring and control of the manufacturing environment;

(c) plant hygiene;

(d) process validation and calibration of analytical apparatus;

(e) training, including the application and principles of quality assurance;

(f) the approval and monitoring of suppliers of materials;

(g) the approval and monitoring of contract manufacturers;

(h) the designation and monitoring of storage conditions for materials and products;

(i) the retention of records;

(j) the monitoring of compliance with good manufacturing practices requirements; and

(k) the inspection, investigation, and taking of samples in order to monitor factors that may affect product quality.

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

(a) to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;

(b) to approve the instructions relating to production operations including the in-process controls, and to ensure their strict implementation;

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

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

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

4.8. **Training:**

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

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

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

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

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

4.9. Personal hygiene:

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

4.9.2. *Practices in personal hygiene:* All personnel shall be trained in hygiene shall be

observed by all those concerned with manufacturing processes, personnel shall be instructed particularly to wash their hands before entering production areas, and signs to this effect shall be pasted and instructions observed.

4.9.3. *Illness:* Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products shall not be allowed to handle starting materials, packaging materials, in-process materials, or drug products until the condition is no longer judged to be a risk.

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

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

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

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

SECTION-5

GOOD PRACTICES IN MANUFACTURING PROCESSING

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

(a) all manufacturing processes which shall be defined are systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;

(b) critical steps of manufacturing processes and any significant changes made to the processes are validate;

(c) all necessary facilities are continued to be made available, including:--
  (i) appropriately qualified and trained personnel;
  (ii) adequate premises and space;
  (iii) suitable equipment and services;
  (iv) correct materials, containers, and labels;
  (v) approved procedures and instructions;
  (vi) suitable storage and transport; and
  (vii) adequate personnel laboratories, and equipment for in-process controls under the responsibility of the production management.

(d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided and followed in letter and spirit;

(e) operators receive training and refresher courses at regular intervals to carry out procedures correctly, and records of such training are maintained;

(f) records are made, manually and or by recording instruments, during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected, and any significant deviations are fully recorded and investigated;

(g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

(h) the proper storage and distribution of the products minimizes any risk to their quality; and

(i) the written system to recall any batch of product from sale or supply is followed whenever a recall is necessitated.

SECTION-6

MATERIALS

6.1. Material, general

6.0.1. *Quarantine:* All incoming materials and finished products shall be quarantined immediately after receipt or processing, until they are released for use or distribution.

6.0.2. *Appropriate storage:* All materials and products shall be stored under the appropriate conditions established by the manufacturer and in an orderly manner to permit batch segregation and stock rotation by a first-in, first-out rule.

6.2. Starting materials

6.2.1. *Purchase:* The purchase of starting materials is an important operation that must involve staff who have a particular and thorough knowledge of the products and suppliers and a pharmacist with some experience of production may be preferred.

6.2.2. *Purchase from producer or established suppliers:* Starting materials shall be purchased directly from the producer or only from established suppliers.

6.2.3. *Checking of containers:* For each consignment, the containers shall be checked for integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels; and, containers shall be cleaned where necessary and labelled, if required, with the prescribed data.

6.2.4. *Damaged container:* Damage to containers and any other problem that might adversely affect the quality of a material shall be recorded and reported to the quality control department and investigated.

6.2.5. *Delivery from different batches:* If a delivery of material is made up of different batches, each batch shall be considered as separate for sampling, testing, and release.

6.2.6. *Labelling:* Starting materials in the storage-area shall be appropriately labelled, and labels shall bear at least the following information, namely: --

(a) the designated name of the product and the internal code reference where applicable.

(b) The batch number(s) given by the supplier and on receipt by the

manufacturer, if any;

(c) Where appropriate, the status of the contents such as on quarantine, on test, released, rejected returned, and recalled, and

(d) Where appropriate an expiry date or a date beyond which retesting is necessary. When fully computerized storage systems are used appropriate system shall be developed for the identification of above-referred information.

6.2.7. *Identity of contents:* There shall be appropriate procedures or measures to ensure the identity of the contents of each container of starting material, and bulk containers from which samples have been drawn shall be identified.

6.2.8. *Released materials to be used:* only starting materials released by the quality control department and within their shelf-life shall be used.

6.2.9. *Correct dispensing:* Starting materials shall be dispensed only by designated persons, following a written procedure to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

6.2.10. *Checking:* Each dispensed material and its weight or volume shall be independently checked and the check recorded.

6.2.11. *Labelling:* Materials dispensed for each batch of the final product shall be kept together and conspicuously labelled as such.

6.3. Packaging materials

6.3.1. *Purchase:* The purchase, handling and control of primary and printed packaging materials shall be as for starting materials.

6.3.2. *Printed materials:* Particular attention shall be paid to printed packaging materials which shall be stored in secure conditions so as to exclude the possibility of unauthorized access, cut labels and other loose printed materials shall be stored and transported in separate closed containers so as to avoid mix-ups and packaging materials shall be issued for use only by designated personnel following an approved and documented procedure.

6.3.3. *Reference numbers:* Each delivery or batch of printed or primary packaging material shall be given a specific reference number or identification mark.

6.3.4. *Obsolete materials:* Outdated or obsolete primary packaging material or printed packaging material shall be destroyed and its disposal be recorded.

6.3.5. *Checking before delivery:* All products and packaging materials to be used shall be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.

6.4. Intermediate and bulk products

6.4.1. *Storage:* Intermediate and bulk products shall be kept under appropriate conditions.

6.4.2. *Handling:* Intermediate and bulk products purchased as such shall be handled on receipt as though they were starting materials.

6.5. Finished pharmaceutical products

6.5.1. *Quarantine:* Finished pharmaceutical products shall be held in quarantine until their final release, and thereafter they shall be stored as usable stock under

conditions established by the manufacturer.

6.5.2. *Release:* The evaluation of finished products and the documentation necessary for release of a product for sale, as per requirement of these rules, shall be followed.

6.6. Rejected and recovered materials

6.6.1. *Storage and disposal:* Rejected materials and products shall be clearly marked as such and stored separately in restricted areas, and they shall either be returned to the suppliers or, where appropriate, reprocessed or destroyed and then action shall be approved by authorized personnel and recorded.

6.6.2. *Reprocessing:* The reprocessing of rejected products shall be exceptional, it is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved and record shall be kept of the reprocessing and a reprocessed batch shall be given a new batch number.

6.6.3. *Batch recovery:* The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture shall be authorized beforehand, this recovery shall be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life and the recovery shall be recorded.

6.6.4. *Additional testing of reprocessed materials:* The need for additional testing of any finished product that has been reprocessed, or into which a recovered product has been incorporated, shall be considered by the quality control department.

6.7. Recalled and returned products

6.7.1. *Recalled products:* Recalled products shall be identified, clearly marked as such and stored separately in a secure area until a decision is taken on their fate.

6.7.2. *Returned goods:* Products returned from the market shall be destroyed unless it is certain that their quality is satisfactory, they may be considered for resale, relabelling, or bulking with a subsequent batch only after they have been critically assessed by the quality control department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued shall be taken into account in this assessment, where any doubt arises over the quality of the product, it shall not be considered suitable for reissue or re-use, although basic chemical reprocessing to recover the active ingredient may be possible, and any action taken shall be appropriately recorded.

6.8. Reagents and culture media

6.8.1. All reagents and culture media shall be recorded upon receipt or preparation.

6.8.2. Reagents made up in the laboratory shall be prepared according to written procedures and appropriately labelled, the label shall indicate the concentration, standardization factor, shelf-life, the date when re-standardization is due, and the storage conditions and the label shall be signed and dated by the person preparing the reagent.

6.8.3. Both positive and negative controls shall be applied to verify the suitability of culture media and the size of the inoculums used in positive controls shall be

appropriate to the sensitivity required.

6.9. Reference standards

6.9.1. *Testing of prepared reference standard:* Reference standards may be available in the form of official reference standards and reference standards prepare red by the producer shall be tested, released, and then stored in the same way as official standards, and they shall be kept under the responsibility of a designated person in a secured area.

6.9.2. *Use:* Official reference standards shall be used only for the purpose described in the appropriate testing method submitted for registration purposes.

6.9.3. *Working standards:*Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization, and all in house reference standards shall be based on official reference standards, when available.

6.9.4. *Storage:* All reference standards shall be stored and used in a manner that will not adversely affect their quality.

6.10. Waste materials

6.10.1. *Storage:* Provision shall be made for the proper and safe storage of waste materials awaiting disposal, and toxic substances and flammable materials shall be stored in suitably designed and separate enclosed cupboards.

6.10.2. *Disposal:* Waste material shall not be allowed to accumulate, and it shall be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

6.10.3. *Effluent Control:* There shall be an effluent control system.

6.11. Miscellaneous

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

SECTION-7

7.1. Processing Operations

7.1.1. *General:* Production *operations must follow clearly defined procedures with the objective of obtaining products of the requisite quality.*

7.1.2. *Material handling:* All handling of materials and products such as receipt and quarantine, sampling, storage, labelling, dispensing, processing, packaging, and distribution shall be done in accordance with written procedures or instructions and where necessary, recorded.

7.1.3. *Avoiding deviation:* Any deviation from instructions or procedures shall be avoided as far as possible and if deviations occur, they shall be approved in writing by a designated person, with the involvement of the quality control department.

7.1.4. *Yield checks:* Check on yields and re-conciliation of quantities shall be carried out as necessary to ensure that yields are within acceptable limits.

7.1.5. *Avoiding mix*-ups: Operations on different products shall not be carried out

simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.

7.1.6. *Labelling:* At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate the rooms used shall be labelled or otherwise identified with an indication of the product or material being processed and its strength, where applicable, and the batch number, and where applicable this indication shall mention the stage of production.

7.1.7. *Un-authorized entry prohibited:* Access to the production premises shall be restricted to authorized personnel.

7.1.8. *In process controls:* In process controls are mostly performed within the production area and they shall not carry any risk for the quality of the product.

7.2. Prevention of cross-contamination and bacterial contamination in production.

7.2.1. *Precautions against dust:* When dry materials and products are used in production, special precautions shall be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitizing materials.

7.2.2. *Measures against contamination:* Contamination of a starting material or of a product by another material or product shall also be avoided and similarly, cross-contamination shall be avoided by appropriate technical or organizational measures, as may be necessary by conducting production segregated areas, namely:-

(a) conducting production in segregated areas;
(b) providing appropriate airlock, pressure differentials and dust extraction;
(c) minimizing the risk of contamination caused by re-circulation or re-entry of untreated or insufficiently treated air;
(d) wearing and keeping protective clothing in areas where products with special risk of cross-contamination are processed;
(e) using, cleaning and decontamination procedures of known effectiveness, as in-effective cleaning of equipment is a common source of cross-contamination;
(f) encourage using a “closed system” of production;
(g) testing for residues where necessary;
(h) using cleanliness status labels on equipment, showing the name of the previous product.

7.2.3. Cross-contamination checks: Measures to prevent cross-contamination and their effectiveness shall be checked periodically according to standard operating procedures.

7.2.4. *Microbiological monitoring:* Production areas where susceptible products are processed shall undergo periodic microbiological monitoring and the bio-burden shall be kept within the specified limits.

7.3. Processing operations, intermediate and bulk products

7.3.1. *Pre-processing cleanliness checks:* Before any processing operation is started, steps shall be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, legal, or documents not

required for the current operation.

7.3.2. *In*-process controls: Necessary in-process controls and environmental controls shall be carried out and recorded.

7.3.3. *Defective equipment:* Means shall be instituted for indicating failures of equipment of services, such as water of gas, to equipment. Defective equipment shall be withdrawn from used until the defect has been rectified.

7.3.4. *Cleaning containers:* Containers for filling shall be cleaned before filling and attention shall be given to avoiding and removing any contaminants such as glass fragments and metal particles. Production equipment shall be cleaned according to detailed written procedures and stored only under clean and dry conditions.

7.3.5. *Yield deviations:* Any significant deviation from the expected yield shall be recorded, and investigated.

7.3.6. *Product pipelines:* Checks shall be carried out to ensure that pipelines and other pieces and equipment used for the transportation of product from one area to another area connected in correct manner.

7.3.7. *Water Pipes:* Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes shall be sanitized according to written procedures that detail the action and limits for microbiological contamination and the measures to be taken.

7.3.8. *Equipment calibration:* Measuring, weighing, recording control equipment and instruments shall be serviced and calibrated at pre-specified intervals and records maintained. To ensure satisfactory functioning instruments shall be checked daily or prior to use for performing analytical tests and the date of calibration and the date when re-calibration is due shall be clearly indicated.

7.3.9. *Repair and maintenance:* Repair and maintenance operations shall not present any hazard to the quality of the products.

7.4. Packaging operations

7.4.1. *Avoiding mix-ups:* When the programme for packaging operations is being set up particular attention shall be given to minimizing the risk of cross-contamination, mix-up, or substitutions, and different products shall not be packaged in close proximity unless there is physical segregation or the use of electronic surveillance.

7.4.2. *Pre- packaging checks*: Before packaging operations are begun, steps shall be taken to ensure that the work area, packaging lines, printing machines, and other, equipment are clean and free from any products, materials, or documents previously used and not required for the current operation, and the line clearance shall be performed according to an appropriate checklist and recorded.

7.4.3. *Labelling of packaging line:* The name and batch number of the product being handled shall be displayed at each packaging station or line.

7.4.4. *Process continuity:* Normally, filling and sealing shall be followed as quickly as possible by labelling and if labelling is delayed, appropriate procedures shall be applied to ensure that no mix-up or mix-labelling can occur.

7.4.5. *Printing operation checks:* The correct performance of any printing, code numbers or expiry dates, done separately or in the course of the packaging shall be checked and recorded, and attention shall be paid to printing by hand which shall be re-checked at regular intervals.

7.4.6. *Label verification:* Special care shall be taken when cut labels are used and when over-printing is carried out off-line and in-hand packaging operations, roll-feed labels are normally preferable to cut labels in helping to avoid mix-up. On-line verification of all labels by automated electronic means can be helpful in preventing mix-up, but checks shall be made to ensure that electronic code readers, label counters, or similar devices are operating correctly.

7.4.7. *Fast colour printing on labels:* Printed and embossed information on packaging materials shall be distinct and resistant to fading or erasing.

7.4.8. *On*-line packaging checks: On-line control of the product during packaging shall include at least check on: --

(a) The general appearance of the packages;
(b) Whether the packages are complete;
(c) Whether the correct product and packaging materials are used;
(d) Whether any over-printing is correct;
(e) The correct functioning the line monitors; and
(f) Samples taken from the packaging line shall not be returned unless inspection is done in close the packaging proximity of line.

7.4.9. *Product re-introduction on packaging line:* Products that have been involved in an unusual event during packaging shall be re-introduced into the process only after special inspection, investigation, and approval by authorized personnel and a detailed record shall be kept of this operation.

7.4.10. *Discrepancies to be investigated:*Any Significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced shall be investigated and satisfactorily accounted for before released.

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

SECTION-8

8. Sanitation and hygiene

Genera: A high level of sanitation and hygiene shall be practiced in every aspect of the manufacture of drug products, the scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product, and potential sources of contamination shall be eliminated through an integrated comprehensive programme of sanitation and hygiene (For sanitation and hygiene please also refer to Section 5 of Schedule B and Section 4, 9 of Schedule B-II).

SECTION-9

9. Validation

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

9.2 **Process Validation to be performed as per written procedures**

9.2.1. *Validation of critical processes:* Critical process shall be validated, prospectively or retrospectively.

9.2.2. *Validation of new master formula:* When any new master formula or method of preparation is adopted, steps shall be taken to demonstrate its suitability for routine processing, and, the defined process, using the materials and equipment specified, shall be shown to yield a product consistently of the required quality.

9.2.3. *Validation of equipment and materials:* Significant amendments to the manufacturing process, including any changer in equipment or materials that may affect product quality and or the reproducibility of the process shall be validated.

SECTION-10

10. Documents

10.1.1. *Maintenance of documents:* Documents, as required under these rules, shall be meticulously maintained and regularly reviewed and kept up to date, and when a document has been revised, a system shall exist to prevent inadvertent use of the superseded version.

10.1.2. *Records of action:* Records of action: Records shall be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. The batch record shall be retained for at least one year after the expiry date of the finished product.

10.1.3. *Documentation systems:* Data may be recorded by electronic data processing systems or by photographic or other reliable means. Master formulate and detailed standard operating procedures relating to the system in use shall be available and the accuracy of the records shall be checked and it documentation is handled by electronic data-processing methods, only authorized persons shall be able to enter or modify data-in the computer, and there shall be a record of changes and deletions, access shall be restricted by passwords or other means and the entry of critical data shall be independently checked and data shall also be readily available.

10.1.4. *States identification:* Labels applied to containers, equipment, or premises shall be unambiguous and in the company's agreed format The labels of different colours may also be used in addition to the wording to indicate the status such as "quarantined" "Accepted," "rejected," or "clear".

10.1.5. *Product labelling:* All finished products shall be labelled in accordance with the Drugs (Labelling and Packing) Rules, 1986.

10.1.6. *Reference standards identification:* For reference standards, the label or accompanying documents shall indicate concentration, date of manufacture, expiry, date, and storage conditions, where appropriate.

10.1.7. *Specification approvals:* Each specification shall be approved and maintained by the by the quality control unit.

10.1.8. *Revision of specification:* Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia or the Drugs (Specifications) Rules, 1978.

10.1.9. *Packaging material specifications:* Packaging material shall conform to specifications, with emphasis placed on the compatibility of the material with the drug product it contains.

10.1.10. Starting material re-assay: Documents describing testing procedures shall state the required frequency for re-assaying each starting material, as determined by its stability.

10.2. Specification for Intermediate and bulk products

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

10.3. Batch processing records

10.3.1. *General:* A batch processing record shall be kept for each batch processed based on the relevant parts of the currently approved master formula, and the method of preparation of such records shall be designed to avoid transcription errors.

10.3.2. *Checking work station:* Before any processing begins, a check shall be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use, and this check shall be recorded.

10.3.3. *Recording process operation:* During processing, the following information shall be recorded at the time each action is taken, and after completion the record shall be dated and signed by the person responsible for the processing operations, namely:-

(a) the name of the product;
(b) the number of the batch being manufactured;
(c) date and times of commencement of significant intermediate stages, and of completion of production;
(d) the name of the person responsible for each stage of production;
(e) the initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g., weighing);
(f) the batch number and or analytical control number and the quantity of each starting material actually weighed including the batch number and amount of any recovered or reprocessed material added;
(g) any relevant processing operation or event and the major equipment used;
(h) the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
(i) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield; and

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

10.4. Batch packaging records

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

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

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

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

10.4.4. *Recording batch number:* Batch-number allocation shall be immediately recorded in a logbook, and the record shall include date of allocation, product identity, and size of batch.

10.4.5. *Analytical records:* Analysis records shall include at least the following, namely:--

(a) the name of the material or product and, where applicable, dosage form;
(b) the batch number and, where appropriate, the manufacturer and/or supplier;
(c) references to the relevant specifications and testing procedures;
(d) test results, including observations and calculations, and reference to any specifications (limits);
(e) dates of testing;
(f) the initials of the persons who performed the testing;

(g) the initials of the persons who verified the testing and the calculations, where appropriate; and
(h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

10.4.6. *Finished product release procedure:* Written release and rejection procedures shall be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.

10.4.7. *Recording batch distribution:* Records shall be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.

10.4.8. *Standard operating procedures:* Standard operating procedures and associated records of action taken or, where appropriate, conclusions reached shall be available at the premises for: --
(a) equipment assembly and validation;
(b) analytical apparatus and calibration;
(c) maintenance, cleaning, and sanitization;
(d) personnel matters including qualification, training clothing, and hygiene;
(e) environmental monitoring;
(f) pest control;
(g) complaints;
(h) recalls; and
(i) returns.

10.4.9. *Equipment logbooks:* Logbooks shall be kept with major and critical equipment as identified by the licensee and shall record, as appropriate, any validations, calibrations, maintenance, cleaning, or repair operations including dates and the identity of the people who carried out these operations.

10.4.10. *Equipment utilization record:* The use of major and critical equipment and the areas where products have been process shall be appropriately recorded in chronological order.

PART II

ADDITIONAL CONDITIONS FOR MANUFACTURE OF STERILE PRODUCTS

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

SECTION-I

1. General

1.1. The production of sterile preparations shall be carried out in clean areas, entry to which shall be through airlocks for personnel and/or for goods clean areas shall be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of an appropriate efficiency.

1.2. The various operations of component preparation (such as containers and

closures), product preparation, filling, and sterilization shall be carried out in separate areas within the clean area.

1.3. Clean areas for the production of sterile products are classified according to the required characteristics of the air, in Grades A, B, C and D as given in the table below:-
TABLE

Air classification system for manufacture of sterile products

Maximum number of particles permitted per m3		Maximum number of viable micro-organisms permitted per m3	
Grade	0.5-5um	75um	
A (laminar-airflow workstation)	3500	None	Less than1
B	3500	None	5
C	350000	2000	100
D	3500000	200000	500

Notes:--

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

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

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

* The guidance given for the maximum permitted number of particles corresponds approximately to the United States Federal Standard 209 E as follow: Class 100 (Grades A and B), Class 10,000 (Grade C), and Class 100,000 (Grade D).

It may not always be possible to demonstrate conformity with particular air standards at the point of fill when filling is in progress, owing to the generation of particles or droplets from the product itself.

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

2. Manufacture of sterile preparation

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

(a) *Terminally sterilized products:* Those in which the preparation is sealed in its final container and terminally sterilized;
(b) *Products sterilized by filtration:*The preparation is sterilized by filtration;
(c) *Products manufactured under aseptic conditions:* Those in which the preparation can be sterilized neither by filtration nor terminally and consequently must be produced from sterile starting materials in an aseptic way.

2.2. **Terminally sterilized products**: Solutions shall generally be prepared in a Grade C environment in order to give low microbial and particulate counts, suitable for immediate filtration and sterilization. Solution preparation could be allowed in a Grade D environment if additional measures are taken to minimize contamination, such as the use of closed vessels. For parenteral, filling shall be done in a laminar-airflow workstation (Grade A) in a Grade C environment. The preparation of other sterile products, e.g. ointments, creams, suspensions, and emulsions, and filling of containers shall generally be done in a Grade C environment before terminal sterilization.

2.3. **Products sterilized by nitration**: The handling of starting materials and the preparation of solutions shall be done in a Grade Environment. These activities could be allowed in a Grade D environment if additional measures are taken to minimize contamination, such as the use of closed vessels prior to filtration. After sterile filtration, the product must be handled and dispensed into containers under aseptic conditions in a Grade A or B area with a Grade B of C background, respectively.

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

3. **Personnel**

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

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

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

3.4. **Hygiene and cleanliness:** High standards of personal hygiene and cleanliness are essential and personnel involved in the manufacture of sterile preparations shall be instructed to report apparent illness or open lesion. Periodic health checks for such conditions are desirable, and actions to be taken about personnel who could be introducing undue microbiological hazard shall be decided by a designated competent person.

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

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

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

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

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

Grade D: The hair and, where appropriate, beard shall be covered, protective clothing and appropriate shoes or long shoes shall be worn, and appropriate measures shall be taken to avoid any contamination coming from outside the clean area.

Grade C: The hair and, where appropriate, beard shall be covered, a shingle or two-piece trouser suit, gathered at the wrists and with a high neck and appropriate shoes or overshoes, shall be worn, and the clothing, shall shed virtually no fibres or particulate matter.

Grade B: Headgear shall totally enclose the hair and, where appropriate, beard; it shall be tucked into the neck of the short, a face mask shall be worn to prevent the shedding of droplets; sterilized non-powdered rubber or plastic gloves and sterilized or disinfected footwear shall be worn; trouser-bottoms shall be tucked inside the footwear and garment sleeves into the gloves, and the protective clothing shall shed virtually no fibres or particulate matter and shall retain particles shed by the body.

SECTION-2

4. Maintenance of clean area

4.1. General: Each manufacturing operation requires an appropriate air cleanliness level in order to minimize the risks of particulate or microbial contamination of the product or materials being handled. Section 1.3 gives the minimum air grades required for different manufacturing operations. The particulate and microbiological conditions as prescribed shall be maintained in the zone immediately surrounding the product whenever the product is exposed to the environment. These conditions shall also be achieved throughout the background environment if no personnel are present in the processing area and if the standards fall for any reason it shall be possible to recover the conditions after a short “clean-up” period. The utilization of absolute-barrier technology and automated systems to minimize human interventions in processing areas can produce significant advantages in ensuring the sterility of

manufactured products, and when such techniques are used the recommendations relating to air quality and monitoring, still apply, with appropriate interpretations of the terms “workstation” and environment.

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

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

4.4. Maintenance of equipment: When equipment maintenance is carried within the clean area, clean instruments and toots shall be used, and the area shall be cleaned and disinfected, where appropriate, before processing recommences, if the required standards of cleanliness and/or asepsis have not been maintained during the maintenance work.

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

6. Sanitation

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

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

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

6.4. Monitoring of clean areas: Clean areas shall be monitored at planned intervals during operations by means of microbial counts of air and surfaces, where aseptic operations are performed, monitoring shall be frequent to ensure that the environment is within specifications,

the results of monitoring shall be considered when batches are assessed for approval, air particulate quality shall also be evaluated on a regular basis, and additional monitoring is sometimes desirable even when there are no production operations such as after validation of systems, cleaning and fumigation.

SECTION-5

7. Processing

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

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

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

(a) They shall simulate as closely as possible actual operations, taking into account such factors as complexity of operations number of personnel working, and length of time;

(b) the medium or media selected shall be capable of growing a wide spectrum of micro-organisms, including those that would be expected to be found in the filling environment; and

(c) they shall include a sufficient number of units of production to give a high degree of assurance that low levels of contamination, if present, would be detected.

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

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

7.5 Activities in clean areas kept minimum: Activities in clean areas, especially when aseptic operations are in progress, shall be kept to a minimum and the movement of personnel

shall be controlled and methodical to avoid excessive shedding of particles and organisms due to over-vigorous activity, and the ambient temperature and humidity shall not be uncomfortably high because of the nature of the garments worn.

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

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

7.8. Care after final cleaning of materials: Components, but product containers and equipment shall handled after the final cleaning process in such a way that they are not decontaminated, and the stage on processing of components, bulk product containers, and equipment shall be properly identified.

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

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

7.11. Bioburden to be minimal: the microbiological contamination of products (bioburden) shall be minimal prior to sterilization, there shall be a working limit on contamination immediately before sterilization that is related to the efficiency of the method to be used and the risk of pyrogens, all solutions, in particular large-volume parenteral, shall be passed through a micro organism relating filter, if possible immediately before the filling process, and where aqueous solutions are held in sealed vessels, any pressure-release outlets shall be protected such as by hydrophobic microbial air filters.

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

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

SECTION-6

8. Sterilization

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

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

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

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

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

9. Sterilization by heat

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

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

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

10. Sterilization by moist heat

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

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

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

11. Sterilization by dry heat

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

12. Sterilization by radiation

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

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

12.3. Measurement of radiation: During the sterilization procedure the radiation dose shall be measured and for this purpose, dosimeters that are independent of dose rate shall be used giving a quantitative measurement of the dose received by the product itself, dosimeters shall be inserted in the load in sufficient number and close enough together to ensure that there is always a dosimeter in the chamber: where plastic dosimeters are used, they shall be used within the time limit of their calibration, dosimeter absorbance shall be read within a short period after exposure to radiation. Biological indicators may be used only as an additional control. Radiation-sensitive colour discs may be used to differentiate between packages that

have been subjected to irradiation and those that have not; they are not indicators of successful sterilization. The information obtained shall constitute part of the batch record, and the total radiation dose shall be administered within a predetermined time span.

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

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

13. Sterilization by ethylene oxide

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

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

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

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

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

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

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

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

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

14.2. Using double filter layer: Owing the potential additional risks of the filtration method as compared with other sterilization processes a double filter layer or second filtration via a further sterilized micro-organism-relating filter immediately prior to filling may be advisable and the final sterile filtration shall be carried out as close as possible to the filling point.

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

14.4. Checking integrity of fitters: The integrity of the filter shall be checked by an appropriate method such as a bubble point test immediately after each use it may also be useful to test the filter in this way before use, the time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter shall be determined during validation and any significant differences from this shall be noted and investigated. Results of these checks shall be recorded in the batch record.

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

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

15. finishing of sterile products

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

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

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

SECTION 7

16. Quality control

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

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

16.2. Sterility test as the last measures: The sterility test applied to the finished product shall be regarded only as the last in a series of control measures by which sterility is assured and can be interpreted only in conjunction with the environmental and batch processing records.

16.3. Monitoring endotoxins: For injectable products, consideration shall be given to mentoring the water and the intermediate and finished product for endotoxins, using an established pharmacopoeial method that has been validated for each typ0e of product, for large-volume infusion solutions, such monitoring of water or intermediates shall always be done in addition to any tests required by the Marketing authorization on the finished product, and when a sample fails a test, the cause of failure shall be investigated and remedial action taken where necessarily.

Saving

This Schedule B-II shall come into force with effect from the date as may be notified by the Federal Government and till such time Schedule B-II as already provided in the Rules shall remain in force.

Schedule B-III

[See Rule 20(b)]

I. PARTICULARS TO BE SHOWN IN MANUFACTURING RECORDS

A. Substances parenteral preparation in genera:

1. Serial Number.
2. Name of the drug.
3. Batch Size.
4. Batch number.
5. Date of commencement of manufacture and date when manufacture was completed.
6. Name of all ingredients, quantities required for the batch size, quantities actually used.
7. Control reference number sin respect of raw materials used in formulation.
8. Date of mixing in case of dry products, e.g., powder, powder mixture for capsule products, etc.

9. Date of granulation wherever applicable.
10. Weight of granules.
11. Date of compression in case of tablets/ date of filling in case of capsules.
12. Date of coating wherever applicable.
13. Records of test to be carried out in case of tablets as under:--
    (a) Average weight every thirty minutes.
    (b) Disintegration time as often as practicable.
14. Records of readings taken to check weight variation in case of capsules.
15. Reference to Analytical Report number stating whether of standard quality or otherwise.
16. Records on the disposal of rejected batches and batches with drawn from the market.
17. Actual production and packing particulars indicating the size and quantity of finished packing.
18. Date of release of finished packing for distribution or sale.
19. In case of Hypodermic tablets and ophthalmic preparations which are required to be manufactured under aseptic conditions, records shall be maintained indicating the precautions taken during the process of manufacture to ensure that aseptic conditions are maintained.
20. Signature of the expert staff responsible for the manufacture.

B. Parenteral preparation:

1. Serial Number.
2. Name of the drug.
3. Batch Size.
4. Batch number (if bulk lot is divided into various batches and processed separately, a batch number distinctly different from that of the bulk lot should be assigned to each of the processed batch).
5. Date of commencement of manufacture and date of completion.
6. Name of all ingredients, quantities required for the lot size, quantities actually used. (All weighing and measurements shall be checked and initialled by the competent person in the section).
7. Control reference numbers in respect of raw materials used.
8. PH of the solution wherever applicable.
9. Date and methods of filtration.
10. Sterility test reference on bulk batch wherever applicable. (If bulk lot is divided into various batches and processed separately, a batch number distinctly different from that of the bulk lot should be assigned to each of the processed batch.
11. Date of filling.
12. Records of tests employed: --
    (a) To ensure that sealed ampules are leak-proof.
    (b) To check the presence of foreign particles.
    (c) For pyrogens wherever applicable.
13. Records of sterilisation in case of parenteral preparation which are heat sterilised including particulars of time temperature and pressure employed.
14. Number and size of containers filed and number rejected.
15. Reference to Analytical Report numbers stating whether of standard quality or otherwise.

16. Records of the disposal of rejected batch and batches with-drawn from the market.
17. Actual production and packing particulars.
18. Date of release finished packing for distribution or sale.
19. Particulars regarding the precautions taken during manufacture to ensure that aseptic conditions are maintained.
20. Control reference numbers in respect of the lot of glass containers used for filling.
21. Signature of the expert staff responsible for manufacture.

[123][C. **Medical Devices:**

1. Serial Number.
2. Name of the Medical Device.
3. Batch Size.
4. Batch Number.
5. Date of commencement of manufacture and date when manufacture was completed.
6. Name of all ingredients, quantities required for the batch size, quantities actually used.
7. Control reference numbers in respect of raw materials used in manufacturing.
8. Record of test to be carried out.
9. Reference to Analytical Report number stating whether of standard quality or otherwise.
10. Record on the disposal of rejected batches and, batches withdrawn from the market.
11. Actual production and packing particulars indicating the size and quantity of finished packing.
12. Date of release of finished packing for distribution or sale.
13. Signature of the expert staff responsible for the manufacture.
14. Sterility test reference on bulk batch where applicable. (If lot is divided into various batches and processed separately, a batch number distinctly different from that of the bulk lot should be assigned to each of the processed batch).
15. Records of test employed, --
16. Records of sterilization
17. Signature of the expert staff responsible for manufacturer.]

II. RECORDS OF RAW MATERIALS

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

III. PARTICULARS TO BE RECORDED IN THE ANALYTICAL RECORDS

A. Tablets and capsules:

1. Analytical report number.

[123]Item C added by SRO 916(I)/2010 dated 30.09..2010

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

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

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

B. Parenteral Preparations

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

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

8. Signature of the Analyst.
9. Opinion and signature of the approved Analyst Pyrogen Tests:-
   1. Test report number.
   2. Name of the sample.
   3. Batch number.
   4. Number of rabbits used.
   5. Weight of each rabbit.
   6. Normal temperature of each rabbit.

7. Mean initial temperature of each rabbit.
8. Dose and volume of solution injected into each rabbit and time of injection.
9. Temperature of each rabbit noted at suitable intervals.
10. Maximum temperature.
11. Response.
12. Summed response.
13. Signature of the Analyst.
14. Opnion and signature of the approved Analyst.

Toxicity Test:

1. Test report number.
2. Name of the Sample.
3. Batch number.
4. Number of mice used and weight of each mouse.
5. Strength and volume of the drug injected.
6. Date of injection.
7. Results and remarks.
8. Signature of Analyst.
9. Opinion and signature of the approved Analyst.

C. For other drugs:

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

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

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

D. Raw materials:

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

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

E. Container, packing material, etc.:-

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

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

7. Remarks.
8. Signature of the examiner.

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

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

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

[124][F. Container, packing material etc.:--

1. Analytical report number.
2. Name of sample.
3. Date of receipt of sample.
4. Date of receipt of sample.
5. Batch number.
   (a) Description.
   (b) Sterility test.
   (c) Pyrogen test, where applicable.
   (d) Bacterial Endotoxin.
   (e) Appearance of solution.
   (f) Acidity ofr alkalinity.
   (g) Absorbance.
   (h) Ethylene Oxide Residue.
   (i) Silicon oil
   (j) Reducing substances.
   (k) Transparency.
   (l) Extractable matters.

[124]Item F added by SRO 916(I)/2010, dated 30.09.2010

(m) Tolerance on graduated capacity.
(n) Graduate scale.
(o) Piston plunger assembly.
(p) Dimensions and finger grip of barrels.
(q) Perofrmance in terms of Dead Space, Integrated or non-intergrated needles.
(r) Where applicable, Auto-Disable features.
(s) Tolerance on nominal capacity.
(t) Fit of the piston in barrel.
(u) Fiducial lines.
(v) Performance after shipping.
(w) Any other tests.

6. Protocols of tests applied:
7. Signature of the Analyst.
8. Opinion and signature of the approved Analyst.]

[SCHEDUE C]

[See Rule 16(c) (iii) and €]

1. Sera.
2. Solution of serum proteins intended for injunction.
3. Vaccines.
4. Toxins.
5. Antigen.
6. Antitoxins.
7. Insulin.
8. Pituitary (Posterior Lobe) Extract.
9. Sterilized surgical signature and sterilized surgical suture.
10. Bacteriophages].

[SCHEDULE D]

[See rule 17(a)]

DRUGS FOR REPACKING

1. Aluminium Hydroxide Gel Dried.
2. Ammonium Bicarbonate.
3. Ammonium Chloride.
4. Ammonium Carbonate.
5. Benzoic Acid.
6. Bismuth Carbonate.
7. Bismuth Subnitrate.
8. Boric Acid.
9. Borax.
10. Caffeine and its salts.

11. Calamine.
12. Calcium Carbonate.
13. Calcium Lactate.
14. Calcium Gluconate.
15. Calcium Hydroxide.
16. Castor Oil.
17. Getrimide Powder.
18. Chloral Hydrate.
19. Ephedrine hydrochloride.
20. Ephedrine Sulphate.
21. Ferrous Sulphate.
22. Ferric Ammonium Citrate.
23. Gentian Violet.
24. Glycerin.
25. Lodine.
26. Ichthammol.
27. Kaolin.
28. Liquid Paraffin Heavy.
29. Magnesium Carbonate.
30. Magnesium Hydroxide.
31. Magnesium Sulphate.
32. Methylene Blue.
33. Magnesium Trisilicate.
34. Methyl Salicylate.
35. Methyl Salicylate.
36. Pix Carb.
37. Potassium Acetate.
38. Potassium Bromde.
39. Potassium Bicarb.
40. Potassium Chloride.
41. Potassium Citrate.
42. Potassium lodine.
43. [Omitted vide SRO 285(I)/2002, dated 22.05.2002]
44. Procaine Hydrochloride
45. Pulv Gentian.
46. Resorcin.
47. Salicylic Acid.
48. Sentonin.
49. Sena.
50. Sodium Benzoate.
51. Sodium bicarbonate.
52. Sodium Chloride.
53. Sodium Bromide.
54. Sodium Carbonate.
55. Sodium Citrate.
56. Sodium lodide.

57. Sodium Metabisuphite.
58. Sodium Potassium Tartrate.
59. Sodium Salicylate.
60. Sodium Sulphate.
61. Sodium Thiosulphate.
62. Soft yellow Paraffin.
63. Sulphanilamide Powder (B.VET.C)
64. Sulphur Precipitated.
65. Sulphur Sublime.
66. Tannic Acid.
67. Zinc oxide.
68. Zinc Sulphate.

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[125][SCHEDULE D-I]

[See Rule (31) 1]

Household remedies including—

Analgesics:

Aspirin and Paracetamol in tables and liquid forms.

(2) Analgesic balms/Plasters.

(3) antiseptics and disinfectants for household use, excluding those containing hormone and antibiotics.

(4) Antidandruff preparations.

Dental preparations.

Antacid and carminatives.

Compound Effervescent Salts, [126][Gripe Waters], Milk of Magnesia.

[127][(7) x x x x x x]

Drugs containing antihistamines and antibiotics or those drugs which are known to be toxic to the human body or are habit forming do not fall under this group.

(8) Contraceptives.

(9) Miscellaneous.

[125]Schedule D-I added vide S.R.O 371(I)/78, dated 8th July, 1978
[126]Omitted vide S.R.O 706(I)/97, dated 5.9.1997.
[127]Serial Number (7) and the entries relating thereto omitted by S.R.O 1330(I)/98, dated 27.11.1998.

Fish Liver Oil and its equivalents.]

SCHEDULE - E

[See Rule 31(10)]

DISEASES, ADVERTISEMENT FOR TREATMENT OF WHICH IS PROHIBITED

1. [Omitted vide S.R.O 871(I)/78, dated 8th July, 1978.]
2. [Omitted vide S.R.O 871(I)/78, dated 8th July, 1978.]
3. Veneral diseases.
4. Sexual importance.
5. Amenorrhoea materorrhagia, memorthagia, metrosalpingitis, ovaritis, fibromas, cysts.
6. Bright's disease, cataract, glaucoma, epilepsy, [128][…..] locomotive ataxia, multiple sclerosis, lupus, paralysis, blindness.
7. Complaints requiring surgical operation (e.g., appendicitis, stomach uncers, prostatic disorders, hernias, sinusitis, mastodites.
8. Serious illness liable to endanger the life of the patient (e.g., pneumonia, pleurisy, abscess of the lungs).

[129][9. Grip Waters"]

[130][10. Cough Preparations.]

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[131][FORM 5-F

[See rule 26 (1)]

Common Technical Document (CTD) for Registration of Human Drugs

Module 1: Administrative Part

Section	Sub-Section	Heading
1.1		Covering Letter and Fee Deposit Slip
1.2		Table of Contents (From Module 1 to Module 5)
1.3		**Applicant Information:**
	1.3.1	Name, address and contact details of Applicant / Marketing Authorization Holder:

[128]Omitted by S.R.O 1330(I)/98, dated 27.11.1998.
[129]New entry added vide SRO 706(I)/97, dated 5.09.1997
[130]Serial no. 10 added by SRO 1330(I)/98, dated 27.11.1998
[131] Added vide SRO 713(I)/2018, dated 08.06.2018

	1.3.2	Name, address and contact details of Manufacturing site.
	1.3.3	Specify whether the Applicant is: a. □ Manufacturer b. □ Importer c. □Is involved in none of the above (contract giver)
	1.3.4	Valid Drug Manufacturing License (DML) of manufacturer / Applicant or Drug Sale License, whichever is applicable.
	1.3.5	Evidence of approval of manufacturing facility / Approved Section from Licensing Authority.
	1.3.6	List of already approved registered drugs in this section.
	1.3.7	Identification of Signature(s) of authorized persons, Incharge Production, Quality Control and Incharge Quality Assurance.
	1.3.8	Manufacturer's Site Master File and Credential (for importer)
1.4		**Type of Application:**
	1.4.1	Application is for the registration of: □ New Drug Product (NDP) □ Generic Drug Product (GDP)
	1.4.1	Pharmaceutical product is intended for: □ Domestic sale. □ Export sale. □ Domestic and Export sales.
	1.4.2	For imported products, please specify one of following: □ Finished Pharmaceutical Product Import. □ Bulk Import and local repacking (specify status of bulk). □ Bulk Import Local Repacking for Export purpose only.
	1.4.3	Contract Manufacturing as per Rule 20-A of Drugs (Licensing, Registering and Advertising) Rules, 1976. □ Domestic Manufacturing. □ Export Purpose Only.

1.5		**Detailed Information of Drug, Dosage From & Labelling Claims:**
	1.5.1	Generic name with chemical name & synonyms of the applied drug.
	1.5.2	Strength / concentration of Active Pharmaceutical ingredient (API) per unit.
	1.5.3	The proposed proprietary name / brand name under which the drug is intended to be sold with trade mark certification / clearance.
	1.5.4	Proposed Pack size and Proposed unit price of drug e.g., per tablet / capsule. Maximum Retail Price (MRP) per pack shall also be mentioned.
	1.5.5	Pharmacotherapeutic Group of Active Pharmaceutical Ingredient (API)
	1.5.6	Pharmacopoeial reference / Status of applied formulation.
	1.5.7	Route of administration.
	1.5.8	For Generic Drug Product, reference of other similar approved medicines with information pertaining to Manufacturer name, brand name, strength, composition, registration number & dosage form, Pack size and Price.
	1.5.9	The registration status of applied drug in same molecule and salt, strength, dosage form, container closure system, indications and route of administration etc. in other countries. The status in reference regulatory authorities is mandatory to mention.
	1.5.10	Dosage form of applied drug.
	1.5.11	Proposed label (outer (secondary) & inner (primary)) & colour scheme in accordance with Drug (Labelling & Packing) Rules, 1986 along with specimens.
	1.5.12	Description of Batch numbering system.
	1.5.13	Training evidence of technical staff with respect of manufacturing of applied drug (mandatory in case of specially designed pharmaceutical product / Novel Dosage Form).
	1.5.14	Summary of Product Characteristics (SmPC) including Prescribing Information (PI) along with Patient information Leaflet (PIL) of the Finished Pharmaceuticals Product (FPP).
	1.5.15	Commitment / Undertaking that after registration of applied drug, the Pharmacovigilance department of the applicant / manufacture is liable to impose similar restrictions, addition of any clinical information (like in Indications, Contra-indications, Side effects, Precautions, Dosage & Adverse Drug Reactions etc. in Summary of Product Characteristics (SmPC), Labelling & Promotional material) or withdraw the drug from market in Pakistan within fourteen days after knowing that such

		information (which was not available or approved by the DRAP at the time of registration) / actions taken (for safety reasons) by any reference / stringent drug regulatory agency / authority & also inform the DRAP (Drug Regulatory Authority of Pakistan) for further action in this regard.
	1.5.16	Commitment / Undertaking that the applicant shall recall the defective Finished Pharmaceutical Products (FPP) and notify the compliance to the authority along with detail of actions taken by him as soon as possible but not more than ten days. The level of recall shall also be defined.
	1.5.17	Commitment / Undertaking that in case of any false claim / concealing of information, the DRAP has the right to reject the application at any time, before and even after approval or registration of the product in case if proved so.
	1.5.18	Commitment / Undertaking that the firm shall follow the official pharmacopoeia specifications for product / substance as published in the latest edition & shall update its specification as per latest editions of the same. In case, the specifications of product / substance not present in any official pharmacopoeia the firm shall establish the specifications. In both cases, the validation of specifications shall be done by the applicant.
	1.5.19	Commitment / Undertaking that in case of any post approval change, the applicant shall ensure that the product with both approvals shall not be available in the market at the same time. And the product with new approvals shall be marketed only after consumption / withdrawal of stock with previous approvals. The company shall be liable to inform the same regarding marketing status of product to the DRAP after getting such post-registration approvals.
	1.5.20	Other commitment e.g., regarding stability studies etc.
	1.5.21	Protocols along with the commitment to follow Good Laboratory Practices (GLP) by the Manufacturer.
	1.5.22	Protocols to implement Good Pharmacovigilance Practice by the Pharmacovigilance department/section of the Manufacturer / Company.
1.6		**Miscellaneous Information:**
	1.6.1	Information on Prior-related Applications.
	1.6.2	Appendix.
	1.6.3	Electronic Review Package.
	1.6.4	QIS (Quality Information Summary).
	1.6.5	Drug Substance related Document including following:

		a. Name and address of API manufacturer. b. Approval of manufacturing facility of API by regulatory body of country & validity. c. Vendor qualification / audit is □ Document based □ Site inspection based d. Reason for point c.

Module 2: (Overviews and Summaries)

Module	Section	Sub-section	Contents
2	2.1		Overall CTD Table of Content
	2.2		CTD Introduction
	2.3		Quality Overall Summary (QOS)*
		2.3	Introduction
		2.3.S	Drug Substance
		2.3.P	Drug Product
		2.3.A	Appendices
		2.3.R	Regional Information
	2.4		Non-Clinical Overview
	2.5		Clinical Overview
	2.6		Non-Clinical Written and Tabulated Summaries (Normally not required for generics)
	2.7		Clinical Summary

***QOS has been explained by a WHO QOS - PD template MODULE 2.3**

Module 3: (Quality / CMC)

Module	Section	Sub-section	Contents
3	3.2.S		DRUG SUBSTANCE

		3.2.S.1	General Information
		3.2.S.2	Manufacture
		3.2.S.3	Characterization
		3.2.S.4	Control of Drug Substance
		3.2.S.5	Reference Standards or Materials
		3.2.S.6	Container Closure System
		3.2.S.7	Stability
	3.2.P		DRUG PRODUCT
		3.2.P.1	Description and Composition of Drug Product
		3.2.P.2	Pharmaceutical Development
		3.2.P.3	Manufacture
		3.2.P.4	Control of Excipient
		3.2.P.5	Control of Drug Product
		3.2.P.6	Reference Standards or Materials
		3.2.P.7	Container Closure System
		3.2.P.8	Stability

Module 3 has been explained by following guidelines M4Q__R1__3, 4_Quality_Questions_Answers_R1 (Location Issues), WHO TRS 970 annexure 4.

Details of Module: 3 (Quality / CMC)

- 3.1 Table of Contents of Module 3
- 3.2 Body of Data
- **3.2.S Drug Substance**
    - **3.2.S.1 General Information**
        - 3.2.S.1.1 Nomenclature
        - 3.2.S.1.2 Structure
        - 3.2.S.1.3 General Properties
    - **3.2.S.2 Manufacture**
        - 3.2.S.2.1 Manufacturer(s)
        - 3.2.S.2.2 Description of Manufacturing Process and Process Controls
        - 3.2.S.2.3 Control of Materials
        - 3.2.S.2.4 Controls of Critical Steps and Intermediates

- 3.2.S.2.5 Process Validation and/or Evaluation
- 3.2.S.2.6 Manufacturing Process Development

❖ **3.2.S.3 Characterisation**
- 3.2.S.3.1 Elucidation of Structure and other Characteristics
- 3.2.S.3.2 Impurities

❖ **3.2.S.4 Control of Drug Substance**
- 3.2.S.4.1 Specification
- 3.2.S.4.2 Analytical Procedures
- 3.2.S.4.3 Validation of Analytical Procedures
- 3.2.S.4.4 Batch Analyses
- 3.2.S.4.5 Justification of Specification

❖ **3.2.S.5 Reference Standards or Materials**

❖ **3.2.S.6 Container Closure System**

❖ **3.2.S.7 Stability**
- 3.2.S.7.1 Stability Summary and Conclusions
- 3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment
- 3.2.S.7.3 Stability Data

- **3.2.P Drug Product**
  - ❖ **3.2.P.1 Description and Composition of the Drug Product**
  - ❖ **3.2.P.2 Pharmaceutical Development**
    - ❖ 3.2.P.2.1**Components of the Drug Product**
      - ❖ 3.2.P.2.1.1 Drug Substance
      - ❖ 3.2.P.2.1.2 Excipients
    - ❖ 3.2.P.2.2 **Drug Product**
      - ❖ 3.2.P.2.2.1 Formulation Development
      - ❖ 3.2.P.2.2.2 Overages
      - ❖ 3.2.P.2.2.3 Physicochemical and Biological Properties
    - ❖ **3.2.P.2.3 Manufacturing Process Development**
    - ❖ **3.2.P.2.4 Container Closure System**
    - ❖ **3.2.P.2.5 Microbiological Attributes**
    - ❖ **3.2.P.2.6 Compatibility**
  - ❖ **3.2.P.3 Manufacture**
    - ❖ 3.2.P.3.1 Manufacturer(s)
    - ❖ 3.2.P.3.2 Batch Formula
    - ❖ 3.2.P.3.3 Description of Manufacturing Process and Process Controls
    - ❖ 3.2.P.3.4 Controls of Critical Steps and Intermediates
    - ❖ 3.2.P.3.5 Process Validation and/or Evaluation
  - ❖ **3.2.P.4 Control of Excipients**
    - ❖ 3.2.P.4.1 Specifications
    - ❖ 3.2.P.4.2 Analytical Procedures
    - ❖ 3.2.P.4.3 Validation of Analytical Procedures
    - ❖ 3.2.P.4.4 Justification of Specifications
    - ❖ 3.2.P.4.5 Excipients of Human or Animal Origin
    - ❖ 3.2.P.4.6 Novel Excipients
  - ❖ **3.2.P.5 Control of Drug Product**
    - ❖ 3.2.P.5.1 Specification(s)

- ❖ 3.2.P.5.2 Analytical Procedures
- ❖ 3.2.P.5.3 Validation of Analytical Procedures
- ❖ 3.2.P.5.4 Batch Analyses - for **Biologics Drugs** & for **Pharmaceutical Drugs**
- ❖ 3.2.P.5.5 Characterisation of Impurities
- ❖ 3.2.P.5.6 Justification of Specification(s)

❖ **3.2.P.6 Reference Standards or Materials**

❖ **3.2.P.7 Container Closure System**

❖ **3.2.P.8 Stability**

- 3.2.P.8.1 Stability Summary and Conclusions
- 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment
- 3.2.P.8.3 Stability Data

- **3.2.A Appendices**
  - 3.2A.1 Facilities and Equipment
  - 3.2.A.2 Adventitious Agents Safety Evaluation
  - 3.2.A.3 Excipients
- **3.2.R Regional Information**
  - ➢ 3.2.R.1 Production Documentation
    Human Blood Product with required supporting documents
  - ➢ 3.2.R.2 TSE Checklist with required supporting documents
  - ➢ 3.2.R.3 Product Interchangeability (Bioequivalence Study Reports)
    - ▪ BE test product uses same DS and DP manufactured at same site as proposed in application
    - ▪ Reference product used in BE study
    - ▪ If BE RP not from same DP site then bridging data (comparative dissolution) will be required
    - ▪ Batch size, manufacturing date & expiry date for test product are stated.
    - ▪ Expiry date & manufacturing site for BE RP (Reference product) are stated.
    - ▪ CoA of both test product and BE RP are provided
    - ▪ IRB & protocol approval are provided
    - ▪ Analytical validation reports are provided
    - ▪ BE inspection report is provided
    - ▪ If BE study is not provided, then justification for bio-wavier is required, with supporting documents
    - ▪ Lot Release Documentation (for Biological Drugs)
  - ➢ 3.2.R.4 Blank Production Batch Record
    - ▪ Yearly Biologic Product Reports (Biological Drugs only)
- **3.3 Literature References**

➢ **Bioequivalence or Comparative Dissolution Testing is discussed in 3.2.P.2.2.1 Formulation Development and 3.2.R.3 Product Interchangeability**

Module 4: (Non-clinical / Safety)

4.1 Table of Contents

4.2 Study Reports

4.2.1 Pharmacology

- 4.2.1.1 Primary Pharmacodynamics
- 4.2.1.2 Secondary Pharmacodynamics
- 4.2.1.3 Safety Pharmacology
- 4.2.1.4 Pharmacodynamic Drug Interactions

4.2.2 Pharmacokinetics

- 4.2.2.1 Analytical Methods and Validation Reports
- 4.2.2.2 Absorption
- 4.2.2.3 Distribution
- 4.2.2.4 Metabolism
- 4.2.2.5 Excretion
- 4.2.2.6 Pharmacokinetic Drug Interactions (non-clinical)
- 4.2.2.7 Other Pharmacokinetic Studies

4.2.3 Toxicology

- 4.2.3.1 Single-Dose Toxicity (in order by species, by route)
- 4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)
- 4.2.3.3 Genotoxicity
  - 4.2.3.3.1 In vitro
  - 4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)
- 4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)
  - 4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
  - 4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity orpharmacokinetics)
  - 4.2.3.4.3 Other studies
- 4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)
  - 4.2.3.5.1 Fertility and early embryonic development
  - 4.2.3.5.2 Embryo-fetal development
  - 4.2.3.5.3 Prenatal and postnatal development, including maternal function
  - 4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.
- 4.2.3.6 Local Tolerance

4.2.3.7 Other Toxicity Studies(if available)

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

4.2.3.7.3 Mechanistic studies (if not included elsewhere)

4.2.3.7.4 Dependence

4.2.3.7.5 Metabolites

4.2.3.7.6 Impurities

4.2.3.7.7 Other

4.3 List of Literature References

Module 5: (Clinical / Efficacy)

- **5.1 Table of Contents of Module 5**
- **5.2 Tabular Listing of All Clinical Studies**
- **5.3 Clinical Study Reports**

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.1 Bioavailability (BA) Study Reports

5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports

5.3.1.3 *In vitro-In vivo* Correlation Study Reports

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

5.3.2.1 Plasma Protein Binding Study Reports

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

5.3.2.3 Reports of Studies Using Other Human Biomaterials

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

5.3.3.2 Patient PK and Initial Tolerability Study Reports

5.3.3.3 Intrinsic Factor PK Study Reports

5.3.3.4 Extrinsic Factor PK Study Reports

5.3.3.5 Population PK Study Reports

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

5.3.4.2 Patient PD and PK/PD Study Reports

5.3.5 Reports of Efficacy and Safety Studies

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

5.3.5.2 Study Reports of Uncontrolled Clinical Studies

5.3.5.3 Reports of Analyses of Data from More Than One Study

5.3.5.4 Other Clinical Study Reports

5.3.6 Reports of Post-Marketing Experience

5.3.7 Case Report Forms and Individual Patient Listings

5.4 Literature References]

[132][SCHEDULE F

[See rule 5(2)]

S./ No.	Item	Grant of Licence	Fee (Rs)	Renewal Fee (Rs)	Remarks
1	2	3	4	5	6
I.	**Drug manufacturing License Fee**	(a) By way of basic	30,000	15,000	If the application for renewal is made before the expiry of the period of validity of license.
		(b) By way of semi-basic	30,000	15,000	
		(c) By way of formulation	100,000	50,000	
		(d) By way of repacking	60,000	30,000	
II.	**Site verification and layout**	(a) Site inspection and verification	5,000	N.A	N.A
		(b) Approval of layout plant	5,000 per section	N.A	N.A
		(c) Revision or extension of layout plant	5,000 per section	N.A	N.A
III.	**Repacking**	Repacking of drugs	5,000 per drug specified in Schedule D	N.A	N.A
IV.	**Drug registration fee**	(a) New drug or molecule / drug not manufactured locally	50,000	20,000	If the application for renewal is made before the expiry of the period of a certificate of registration.
		(b) Any other drug for import	100,000	20,000	
		(c) Drug for local manufacture	20,000	10,000	
		(d) Drug for import	--	40,000	If the application for renewal is made after the expiry of the period for a certificate o
		(e) Drug for local manufacture	--	20,000	

[132] Substituted vide SRO 117(I)/2012 dated 10, September, 2012

					registration but within sixty days after the expiry of the period of validity.
		Variance to registration application i.e. changes in inactive raw materials, method of manufacture, testing methods or quality specification, product specification, packing materials including change of labeling specification, etc	5,000	--	N.A
V.	**For the grant of additional pack (Price Fixation)**	Any drug for local manufacture or import	5,000	--	N.A
VI.	**For advertisement**	(a) Per advertisement to print media	10,000	--	N.A
		(b) Per advertisement for Radio/ Audio	15,000	--	N.A
		(C) Per advertisement for T.V/Cinema	25,000	--	N.A
VII.	**For price increase**	Any drug for local manufacture or import (human)	20,000	--	N.A
VIII.	**Miscellaneous applications**	Any other application having commercial significance	5,000	--	N.A

Schedule G

[133][**See rule 30 (11)**]

ETHICAL CRITERIA FOR MEDICINAL DRUG PROMOTION

1. Promotion of drugs.- (1) For the purposes of this Schedule, "promotion" means all informational and persuasive activities by manufacturer and distributors, the effect of which is to induce the prescription, supply, purchase and/or use of medicinal drugs.

[133] Added vide S.R.O. 1362(I)/96 dated 28.11.1997.

(2) All claims concerning a drug for the purposes of promotion shall be reliable, accurate, truthful; informative, balanced, up to date, capable of substantiation and in good taste. Such claims shall not contain misleading, unverifiable statements, omissions likely to induce medically unjustifiable use of a drug or to give rise to under risks. The word "safe" shall not be used with respect to promotion unless properly qualified. Comparison of products shall be factual, fair and capable of substantiation.

Promotional material shall not be designed so as to disguise its real nature.

(3) Scientific data in the public domain shall be made available, on request, to prescribers and any other person entitled to receive it as appropriate to their requirements. Promotion in the form of financial or material benefits shall not be offered to or sought by health care practitioners to influence them in the prescription of drugs.

2. Advertisements in any form made to physicians and health-related professionals.- (1) The wording and illustrations in advertisements to physicians and related health professionals shall be fully consistent with the approved scientific data sheet for the drug concerned or other source of information with similar content. The text shall be fully legible.

(2). While introducing the drug to the physician for the first time in shall contain full product information, on the basis of the approved scientific data sheet or similar document and shall contain, among others, the following information:-

(a) The generic name(s) of the active ingredient(s);
(b) the content of active ingredient(s) per dosage form or regimen;
(c) the generic name(s) of other ingredient(s) known to cause problem(s)
(d) the approved therapeutic uses;
(e) dosage form or regimen;
(f) side-effects and major adverse drug reactions;
(g) precautions, contra-indications and warnings;
(h) major interactions;
(i) the name and address of manufacturer or distributor;
[--]
(j) reference to appropriate scientific literature ; and
(k) Price of the drug, ; and

(3) Reminder advertisements shall include, amongst others, at least the international non-proprietary name or generic name, the name of each active ingredient and the price of drug and the name and address for the manufacturer or distributor for the purpose of receiving further information.

3. Advertisements in any form to the general public.- (1) Advertisements to the general public, where permissible, shall help people to make rational decisions on the use of drugs determined to be legally available without a prescription. While advertisements shall take account of people's legitimate desire for information regarding their health they shall not take undue advantage of people's concern about their own health. Advertisement shall not generally be permitted for prescription drugs or to promote drugs for certain serious conditions that can be treated only by qualified health practitioners. The scheduled narcotic and psychotropic drugs shall not be advertised to the general public in connection with fight against drug addiction and dependency. Although health education aimed at children is highly desirable, drug advertisements shall not be directed at children. Promotional material shall be factual and claims for cure, prevention or relieve of an ailment shall be made only if this can be substantiated. Advertisements shall also indicate, where applicable, appropriate limitations to the use of the drug.

(2) When lay language is used the information shall be consistent with the approved scientific data or other legally determined scientific basis for approval. Language which brings about fear or distress shall not be used.

(3) Taking into account the media employed, advertisements to the general public may amongst others, contain, he following information:-

(a) The generic name(s) of the active ingredient(s);

(b) major indication(s) for use; (S.R.O. 1362(I)/96-28.11.96).

(c) major precautions, contra-indications and warnings, if any; and

(d) name of manufacturer or distributor.

4. Information on price to the consumer shall be accurately and honestly portrayed.

4. Medical Representatives.- (1) Medical representatives shall have an appropriate educational background. They shall be adequately trained so as to posses sufficient medical and technical knowledge and integrity to present information on products and carry out other promotional activities in an accurate and responsible manner. Employers shall be responsible for the basic and continuing training of their representatives. The training shall include instructions regarding appropriate ethical conduct taking into consideration the W.H.O. criteria.

(2) Medical representatives shall make available to prescribers and dispensers complete and unbiased information for each product discussed, such as an approved scientific data or other source of information with similar contents.

(3) Employers shall be responsible for the statements and activities of their medical, representatives. Medical representative shall not offer inducements to prescribers and dispensers. Prescribers and dispenses shall not solicit such inducements. In order to avoid over-promotion, the main part of the volume of sales they generate.

5. Free samples of prescription drugs for promotional purposes.- Free samples of drugs may be provided in modest quantities to prescribers, preferably on request.

6. Free samples of non-prescription drugs to the general public for promotional purposes.- There shall be no free sampling of non-prescription drug to the general public for promotional purposes.

7. Symposia and other scientific meetings.- The intimation regarding scientific symposia, seminars, conferences and such meetings where sponsored by a pharmaceutical manufacturer or distributor shall be clearly communicated in advance. The invitation letter should accurately reflect the presentations and discussions to be held. Entertainment or other hospitality, offered to members of the medical and allied professions shall be secondary to the main purpose of the meeting and shall be kept to a modest level.

8. Post-marketing scientific studies, surveilance and disseminaion of information.- (1) The Registration Board shall be made aware of any post-marketing clinical trials for drugs that are conducted and the results thereafter as soon as possible.

(2) Post-marketing scientific studies and surveillance shall not be misused as a disguised form of promotion.

(3) Substantiated information on hazards associated with the drug shall be reported to the Registration Board as a priority.

9. Packaging and labelling.- Appropriate information being important to ensure the rational use of drugs, all packaging and labelling material shall provide information consistent with that approved by the Registration Board and if no such approval is available it shall be, consistent with that approved by the drug regulatory authority of the country from which the

drug is imported or other reliable sources of information with similar content. Any wording and illustration on the package and label shall conform to the principles of ethical criteria enunciated in this Schedule.

10. Information for patients contained in package inserts, leaflets and booklets.- (1) Adequate information on the use of drugs shall be made available to the patients where it is necessary for rational use of a drug. In package inserts or leaflets the manufacturers or distributors shall ensure that the information reflected is correct. If package inserts or leaflets are used for promotional purposes, they shall comply with the ethical criteria enunciated in this Schedule. The wording of the package inserts or leaflets, if prepared specially for patients, shall be in lay language subject to the condition that the medical and scientific content is properly reflected.

(2) In addition to approved package inserts and leaflets wherever available the preparation and distribution of booklets and other information material for patients and consumer shall also comply with the ethical criteria enunciated in this schedule.

[134][SCHEDULE-H]

1. Contract production and analysis.--

1.1 Contract manufacture or analysis shall be undertaken by a manufacturer (contract acceptor) that holds a valid drug manufacturing licence and shall have adequate manufacturing, quality control and quality assurance facilities, knowledge, experience and competent personnel to satisfactorily carry out the manufacture or analysis of registered drug product.

1.2 For sale in Pakistan, relevant provisions of the Drugs Act, 1976, the Drug Regulatory Authority of Pakistan Act, 2012 and rules framed thereunder shall be followed. For manufacturing of products for export purpose, manufacturing and analysis may be carried out as per product specification given by the contract giver.

1.3 There shall be a written quality agreement between contract giver and contract acceptor (drawn by the people having suitable knowledge in manufacturing, quality control and quality assurance requirements). The contract shall clearly establish the duties of each party. The quality management system of contract giver must clearly state responsibilities and the way in which the authorized person of each party shall exercise

[134]Substituted vide SRO 1347(I)/2021 15.10.2021.

full responsibility in releasing each batch of product for sale or issuing the certificate of analysis. A copy of such contract shall be provided along with registration application.

1.4 The contract shall have explicit provision for auditing the facilities of the contract acceptor and contract giver at any time to ensure that manufacturing or analysis of contracted products are being done as per specifications and the contract.

1.5 Approval for release to sell the product shall be given by the authorized person as mentioned in the contract. This authorization shall be in addition to the product released by the contract manufacturer.

2. Contract giver.--

2.1 The contract giver before submission of application for contract manufacturing permission shall be responsible for assessing the legality, suitability and competence of the contract acceptor in successfully carrying out the work or tests required and for ensuring that the principles of good manufacturing practices are followed.

2.2 Upon receiving of contract manufacturing or analysis application, the Registration Board may cause to inspect the manufacturing or analysis facility of contract acceptor by a panel of experts as determined by the Board to verify the report submitted by contract giver, evaluation of cGMP compliance for manufacturing, quality control, validation, stability and storage facilities of both contract giver and contract acceptor etc.

2.3 The contract giver shall provide the contract acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the registration and any other legal requirements and the contract giver shall ensure that the contract acceptor is fully aware of any problem associated with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials or other products. Contract giver shall ultimately be responsible to ensure that processes are in place and complied with during contract manufacturing period and shall inform Registration Board in case of any breach of any facility of the contract.

2.4 The contract giver shall ensure that all processed products and materials delivered by the contract acceptor comply with their specifications or that the product has been released by the authorized persons.

3. Contract acceptor.—

3.1 The contract acceptor must have adequate premises, equipment, knowledge, facilities, experience and competent personnel to carry out satisfactorily the work ordered by the contract giver.

3.2 The contract acceptor shall not pass to a third party any of the work entrusted to him under the contract without the written consent of the contract giver and arrangements made between the contract acceptor and any third party shall ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract acceptor.

3.3 The contract acceptor shall refrain from making any change outside the terms of the contract or any activity that may adversely affect the quality of the product manufactured, packed and analyzed for the contract giver.

3.4 Any change required in manufacturing process, raw or packaging material by the contract acceptor shall be made through a change control mechanism approved by both contract giver and acceptor and properly validated through required processes like stability testing, validation etc. before the product is produced after change and is released for sale.

3.5 Contract acceptor is responsible for keeping the record of production and analysis. Both the contract giver and the contract acceptor shall retain sufficient number of samples of each batch to allow double testing of product, till the expiry of the product for reference. The record shall be made accessible to the contract giver or Registration Board or any other investigating agency etc. at all times for the purpose of compliance to law.

3.6 Contract manufacturer shall submit details of production of each batch of drug manufactured under contract on Form-7 to the Registration Board quarterly, as required by Drugs (Licensing, Registering and Advertising) Rules, 1976.

3.7 In case of change of source of raw material and machinery by the contract manufacturer, proper validation and stability study shall be conducted and recorded for cGMP compliance.

4. The contract.—

4.1 A contract shall be drawn up between the contract giver and contract acceptor that shall specify their respective responsibilities including but not limited to procurement, import, sampling, analysis, manufacture, quality control including in-process controls, quality assurance, quality management system, market release, knowledge management, technology transfer, supply chain, record keeping, retention samples, complaint handling, pharmacovigilance, rejection, recall including undertaking to

comply with the Drugs Act, 1976, the Drug Regulatory Authority of Pakistan Act, 2012 and rules framed thereunder. However, import of raw and packing materials for manufacturing of registered drugs shall be responsibility of contract acceptor or contract giver as per their mutual agreement.

5. Miscellaneous.—

5.1 Fee for grant, renewal/extension and pre and post registration variation in contract manufactured products shall be applicable as determined by Authority with the approval of Policy Board.

5.2 Contravention to any provision of the Drug Regulatory Authority of Pakistan Act, 2012, the Drugs Act, 1976 and rules made thereunder including Schedule-H, or any condition of registration by the contract giver or contract acceptor shall be placed before the Registration Board for appropriate decision as per law.

5.3 If any drug manufactured on contract basis is found or reported in contravention of any of the provisions of the Drugs Act, 1976 and rules made thereunder, then both the contract giver and acceptor shall be liable to any action under the said Act and rules.

5.4 Apart from compliance to the Drug (Labeling and Packaging) Rules, 1986, name, address, and drug manufacturing licence number (in case of manufacturer) or drug sale licence number (in case of foreign pharmaceutical company) of contract giver, shall also appear on all labels and packaging materials.

5.5 Contract manufactured products registered for export purpose shall not be permitted for sale in Pakistan. In case of violation, contract manufacturing permission shall be withdrawn in addition to other legal proceedings. Moreover, exporter shall also furnish confirmation about receiving of stock in importing country after export.

5.6 Change of contract manufacturer shall be allowed during contract period only on genuine reasons including Force Majeure, the fee for this shall be seventy-five thousand rupees per product. New contract manufacturer shall ensure the stability and validation of the product and all other quality assurance specifications. If the previous contract manufacturer is still manufacturing the drug after change of its status, then it would be treated as spurious drug and would be dealt with under relevant provision of the Drugs Act, 1976 or the Drug Regulatory Authority of Pakistan Act, 2012.]