MINISTRY OF HEALTH AND FAMILY WELFARE

(Department of Health and Family Welfare)

NOTIFICATION

New Delhi, the 19th March, 2019

G.S.R.227(E) .— WHEREAS the draft of the New Drugs and Clinical Trials Rules, 2018 was published, in exercise of the powers conferred by sub-section (1) of section 12 and sub-section (1) of section 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), in the Gazette of India, Extraordinary, Part II, section 3, sub-section (i) *vide* notification number G.S.R. 104(E), dated the 1st February, 2018, by the Central Government, after consultation with the Drugs Technical Advisory Board, inviting objections and suggestions from all persons likely to be affected thereby, before the expiry of a period of forty-five days from the date on which copies of the Official Gazette containing the said notification were made available to the public;

AND WHEREAS, copies of the Official Gazette containing the said notification were made available to the public on the 7th February, 2018;

AND WHEREAS, all objections and suggestions received in response to the said draft notification have been duly considered by the Central Government;

AND WHEREAS, the Hon'ble Supreme Court of India in Writ Petition(s) (Civil) No (s). 33/2012 Swathaya Adhikar Manch, Indore and another Versus Union of India and others with W.P.(C) No. 79/2012 (PIL-W), *inter alia,* observed that new clinical trial rules shall be finalised urgently;

NOW, THEREFORE, in exercise of the powers conferred by section 12 and section 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government, after consultation with the Drugs Technical Advisory Board, hereby makes the following rules, namely:—

CHAPTER I

PRELIMINARY

1. Short title, commencement and applicability.— (1) These rules may be called the New Drugs and Clinical Trials Rules, 2019.

(2) They shall come in to force from the date of their publication in the Official Gazette, except Chapter IV which shall come in to force after one hundred and eighty days.

(3) They shall apply to all new drugs, investigational new drugs for human use, clinical trial, bioequivalence study, bioavailability study and Ethics Committee.

2. Definitions.— (1) In these rules, unless the context otherwise requires,—

(a) "academic clinical trial" means a clinical trial of a drug already approved for a certain claim and initiated by any investigator, academic or research institution for a new indication or new route of administration or new dose or new dosage form, where the results of such a trial are intended to be used only for academic or research purposes and not for seeking approval of the Central Licencing Authority or regulatory authority of any country for marketing or commercial purpose;

(b) "Act" means the Drugs and Cosmetics Act, 1940 (23 of 1940);

(c) "active pharmaceutical ingredient" means any substance which can be used in a pharmaceutical formulation with the intention to provide pharmacological activity; or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease; or to have direct effect in restoring, correcting or modifying physiological functions in human beings or animals;

(d) "adverse event" means any untoward medical occurrence (including a symptom or disease or an abnormal laboratory finding) during treatment with an investigational drug or a pharmaceutical product in a patient or a trial subject that does not necessarily have a relationship with the treatment being given;

(e) "bioavailability study" means a study to assess the rate and extent to which the drug is absorbed from a pharmaceutical formulation and becomes available in the systemic circulation or availability of the drug at the site of action;

(f) "bioequivalence study" means a study to establish the absence of a statistically significant difference in the rate and extent of absorption of an active ingredient from a pharmaceutical formulation in comparison to the reference formulation having the same active ingredient when administered in the same molar dose under similar conditions;

(g) "bioavailability and bioequivalence study centre" means a centre created or established to undertake bioavailability study or bioequivalence study of a drug for either clinical part or for both clinical and analytical part of such study;

(h) "biomedical and health research" means research including studies on basic, applied and operational research or clinical research, designed primarily to increase scientific knowledge about diseases and conditions (physical or socio-behavioral); their detection and cause; and evolving strategies for health promotion, prevention, or amelioration of disease and rehabilitation but does not include clinical trial as defined in clause (j);

(i) "Central Licencing Authority" means the Drugs Controller, India as referred to in rule 3;

(j) "clinical trial" in relation to a new drug or investigational new drug means any systematic study of such new drug or investigational new drug in human subjects to generate data for discovering or verifying its,-

(i) clinical or;

(ii) pharmacological including pharmacodynamics, pharmacokinetics or;

(iii) adverse effects,

with the objective of determining the safety, efficacy or tolerance of such new drug or investigational new drug;

(k) "clinical trial protocol" means a document containing the background, objective, rationale, design, methodology including matters concerning performance, management, conduct, analysis, adverse event, withdrawal, statistical consideration and record keeping pertaining to clinical trial;

(l) "clinical trial site" means any hospital or institute or any other clinical establishment having the required facilities to conduct a clinical trial;

(m) "efficacy" in relation to a drug means its ability to achieve the desired effect in a controlled clinical setting;

(n) "effectiveness" in relation to a drug means its ability to achieve the desired effect in a real world clinical situation after approval of the drug;

(o) "Ethics Committee" means, for the purpose of, -

(i) clinical trial, Ethics Committee, constituted under rule 7 and registered under rule 8;

(ii) biomedical and health research, Ethics Committee, constituted under rule 16 and registered under rule 17;

(p) "Good Clinical Practices Guidelines" means the Good Clinical Practices Guidelines for conduct of clinical studies in India, formulated by the Central Drugs Standard Control Organisation and adopted by the Drugs Technical Advisory Board;

(q) "global clinical trial" means any clinical trial which is conducted as part of a clinical development of a drug in more than one country;

(r) "investigational new drug" means a new chemical or biological entity or substance that has not been approved for marketing as a drug in any country;

(s) "investigational product" means the pharmaceutical formulation of an active ingredient or placebo being tested or used in a clinical trial;

(t) "investigator" means a person who is responsible for conducting clinical trial at the clinical trial site;

(u) "medical management" means treatment and other necessary activities for providing the medical care to complement the treatment;

(v) "new chemical entity" means any substance that has not been approved for marketing as a drug by a drug regulatory authority of any country including the authorities specified under these rules and is proposed to be developed as a new drug for the first time by establishing its safety and efficacy;

(w) "new drug" means,—

(i) a drug, including active pharmaceutical ingredient or phytopharmaceutical drug, which has not been used in the country to any significant extent, except in accordance with the provisions of the Act and the rules made thereunder, as per conditions specified in the labelling thereof and has not been approved as safe and efficacious by the Central Licencing Authority with respect to its claims; or

(ii) a drug approved by the Central Licencing Authority for certain claims and proposed to be marketed with modified or new claims including indication, route of administration, dosage and dosage form; or

(iii) a fixed dose combination of two or more drugs, approved separately for certain claims and proposed to be combined for the first time in a fixed ratio, or where the ratio of ingredients in an approved combination is proposed to be changed with certain claims including indication, route of administration, dosage and dosage form; or

(iv) a modified or sustained release form of a drug or novel drug delivery system of any drug approved by the Central Licencing Authority; or

(v) a vaccine, recombinant Deoxyribonucleic Acid (r-DNA) derived product, living modified organism, monoclonal anti-body, stem cell derived product, gene therapeutic product or xenografts, intended to be used as drug;

Explanation.— The drugs, other than drugs referred to in sub-clauses (iv) and (v), shall continue to be new drugs for a period of four years from the date of their permission granted by the Central Licencing Authority and the drugs referred to in sub-clauses (iv) and (v) shall always be deemed to be new drugs;

(x) "orphan drug" means a drug intended to treat a condition which affects not more than five lakh persons in India;

(y) "pharmaceutical formulation" means any preparation for human or veterinary use containing one or more active pharmaceutical ingredients, with or without pharmaceutical excipients or additives, that is formulated to produce a specific physical form, such as, tablet, capsule or solution, suitable for administration to human or animals;

(z) "pharmacovigilance" means the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other drug- related problem;

(aa) "phytopharmaceutical drug" means a drug of purified and standardised fraction, assessed qualitatively and quantitatively with defined minimum four bio- active or phytochemical compounds of an extract of a medicinal plant or its part, for internal or external use on human beings or animals, for diagnosis, treatment, mitigation or prevention of any disease or disorder but does not include drug administered through parenteral route;

(bb) "placebo" means an inactive substance visually identical in appearance to a drug being tested in a clinical trial;

(cc) "post-trial access" means making a new drug or investigational new drug available to a trial subject after completion of clinical trial through which the said drug has been found beneficial to a trial subject during clinical trial, for such period as considered necessary by the investigator and the Ethics Committee;

(dd) "registered pharmacist" shall have the meaning as assigned to it in clause(i) of section 2 of the Pharmacy Act, 1948 (8 of 1948);

(ee) "Schedule" means the Schedule annexed to these rules;

(ff) "serious adverse event" means an untoward medical occurrence during clinical trial resulting in death or permanent disability, or hospitalisation of the trial subject where the trial subject is an outdoor patient or a healthy person, prolongation of hospitalisation where the trial subject is an indoor-patient, persistent or significant disability or incapacity, congenital anomaly, birth defect or life threatening event;

(gg) "similar biologic" means a biological product which is similar in terms of quality, safety and efficacy to reference biological product licenced or approved in India, or any innovator product approved in International Council of Harmonisation (ICH)member countries;

(hh) "sponsor" includes a person, a company or an institution or an organisation responsible for initiation and management of a clinical trial;

(ii) "State Licencing Authority" means Licencing Authority appointed by a State Government having qualifications specified in rule 49A of the Drugs and Cosmetics Rules, 1945;

(jj) "trial subject" means a person who is either a patient or a healthy person to whom investigational product is administered for the purposes of a clinical trial.

(2) Words and expressions used in these rules but not defined herein but defined in the Drugs and Cosmetics Act, 1940 (23 of 1940) shall have the meaning assigned to them in the Act.

CHAPTER II

AUTHORITIES AND OFFICERS

3. Central Licencing Authority.— The Drugs Controller, India appointed by the Central Government in the Ministry of Health and Family Welfare shall be the Central Licencing Authority for the purposes of these rules.

4. Delegation of powers of Central Licencing Authority.— (1) The Drugs Controller, India, with the prior approval of the Central Government, may, by an order in writing, delegate all or any of powers of the Central Licencing Authority to any other officer of the Central Drugs Standard Control Organisation not below the rank of Assistant Drugs Controller (India).

(2) The officer to whom the powers have been delegated under sub-rule (1) shall exercise all or any of the powers of the Central Licencing Authority under its name and seal.

5. Controlling Officer.— (1) The Drugs Controller, India may designate any officer not below the rank of Assistant Drugs Controller (India) as Controlling Officer.

(2) The Drugs Controller, India shall, by order, specify the areas and powers of the Controlling Officer.

(3) The Controlling Officer, designated under sub-rule (1) shall supervise the work of subordinate officers and shall exercise powers and perform functions which may be assigned to that Officer.

CHAPTER III

ETHICS COMMITTEE FOR CLINICAL TRIAL, BIOAVAILABILITY AND BIOEQUIVALENCE STUDY

6. Requirement of the Ethics Committee.— (1) Whoever intends to conduct clinical trial or bioavailability study or bioequivalence study shall be required to have approval of an Ethics Committee for clinical trial registered under rule 8.

(2) The Ethics Committee shall apply for registration with the Central Licencing Authority under rule 8.

7. Constitution of Ethics Committee for clinical trial.— (1) The Ethics Committee shall have a minimum of seven members from medical, non-medical, scientific and non-scientific areas with at least**,—**

(i) one lay person;

(ii) one woman member;

(iii) one legal expert;

(iv) one independent member from any other related field such as social scientist or representative of non-governmental voluntary agency or philosopher or ethicist or theologian.

(2) The Ethics Committee referred to in sub-rule(1) shall consist of at least fifty percent of its members who are not affiliated with the institute or organization in which such committee is constituted.

(3) One member of the Ethics Committee who is not affiliated with the institute or organization shall be the Chairperson, and shall be appointed by such institute or organisation.

(4) One member who is affiliated with the institute or organization shall be appointed as Member Secretary of the Ethics Committee by such Institute or organization.

(5) The committee shall include at least one member whose primary area of interest or specialisation is non-scientific and at least one member who is independent of the institution.

(6) The members of the Ethics Committee shall follow the provisions of these rules, Good Clinical Practices Guidelines and other regulatory requirements to safeguard the rights, safety and well-being of trial subjects.

(7) Every member of the Ethics Committee shall be required to undergo such training and development programmes as may be specified by the Central Licencing Authority from time to time:

Provided that any member, who has not successfully completed such training and developmental programmes, shall be disqualified to hold the post of member of the Ethics Committee and shall cease to be a member of such committee.

(8) The members representing medical scientists and clinicians shall possess at least post graduate qualification in their respective area of specialisation, adequate experience in the respective fields and requisite knowledge and clarity about their role and responsibility as committee members.

(9) As far as possible, based on the requirement of research area such as Human Immunodeficiency Virus (HIV) or genetic disorder, specific patient group may also be represented in the Ethics Committee.

(10) No member of an Ethics Committee, having a conflict of interest, shall be involved in the oversight of the clinical trial or bioavailability or bioequivalence study protocol being reviewed by it and all members shall sign a declaration to the effect that there is no conflict of interest.

(11) While considering an application which involves a conflict of interest of any member of the Ethics Committee, such member may voluntarily withdraw from the Ethics Committee review meeting, by expressing the same in writing, to the Chairperson.

(12) The details in respect of the conflict of interest of the member shall be duly recorded in the minutes of the meetings of the Ethics Committee.

8. Registration of Ethics Committee relating to clinical trial, bioavailability and bioequivalence study.— (1) Every Ethics Committee, constituted under rule 7, shall make an application for grant of registration to the Central Licencing Authority in Form CT-01.

(2) The Ethics Committee shall furnish such information and documents as specified in Table 1 of the Third Schedule along with the application made in Form CT-01.

(3) The Central Licencing Authority,—

(i) shall scrutinise the information and documents furnished with the application under sub-rule (2); and

(ii) make such further enquiry, if any, considered necessary and after being satisfied, that the requirements of these rules have been complied with, may grant registration to Ethics Committee in Form CT-02; and if the Central Licencing Authority is not satisfied with the compliance of these rules by the applicant Ethics Committee, it may, reject the application, for reasons to be recorded in writing, within a period of forty-five working days, from the date of the receipt of the application made under sub-rule (1).

(4) An applicant Ethics Committee aggrieved by the decision of rejection of the application by the Central Licencing Authority under clause (ii) of sub-rule (3), may file an appeal before the Central Government in the Ministry of Health and Family Welfare within sixty working days from the date of the receipt of order of such rejection.

(5) The Central Government may, after such enquiry, as considered necessary, and after giving an opportunity of being heard to the appellant referred to in sub-rule (4), shall dispose of the appeal filed under that sub-rule within a period of sixty working days from the date on which the appeal has been filed.

9. Validity period of registration of Ethics Committee for clinical trial.— The registration granted in Form CT-02 shall remain valid for a period of five years from the date of its issue, unless suspended or cancelled by the Central Licencing Authority.

10. Renewal of registration of Ethics Committee for clinical trial.— (1) On expiry of the validity period of registration granted under rule 9, an Ethics Committee may make an application for renewal of registration in Form CT-01 along with documents as specified in Table 1 of the Third Schedule ninety days prior to the date of the expiry of the registration:

Provided that if the application for renewal of registration is received by the Central Licencing Authority ninety days prior to the date of expiry, the registration shall continue to be in force until an order is passed by the said authority on such application:

Provided also that fresh set of documents shall not be required to be furnished, if there are no changes in such documents furnished at the time of grant of registration, and the applicant renders a certificate to that effect indicating that there is no change.

(2) The Central Licencing Authority shall, after scrutiny of information furnished with the application and after taking into account the inspection report, if any, and after such further enquiry, as considered necessary, and on being satisfied that the requirements of these rules have—

(i) been complied with, renew the registration of Ethics Committee in Form CT-02;

(ii) not been complied with, reject the application, for reasons to be recorded in writing, within a period of forty-five working days from the date of renewal application made under sub-rule (1).

11. Functions of Ethics Committee.— The Ethics Committee for clinical trial shall perform the following functions for a person, institution or organization; namely:—

(i) review and accord approval to a clinical trial, bioavailability or bioequivalence study protocol and other related documents, as the case may be, in the format specified in clause (B) of Table 1 of the Third Schedule and oversee the conduct of clinical trial to safeguard the rights, safety and wellbeing of trial subjects in accordance with these rules, Good Clinical Practices Guidelines and other applicable regulations;

(ii) make at appropriate intervals, an ongoing review of the clinical trials for which it has accorded approval and such review may be based on periodic study progress reports furnished by the investigators or monitoring and internal audit reports furnished by the sponsor or by visiting the study sites;

(iii) indicate the reasons that weighed with it while rejecting or asking for a change or notification in the protocol in writing and a copy of such reasons shall also be made available to the Central Licencing Authority;

(iv) where any serious adverse event occurs to a trial subject or to study subject during clinical trial or bioavailability or bioequivalence study, the Ethics Committee shall analyse the relevant documents pertaining to such event and forward its report to the Central Licencing Authority and comply with the provisions of Chapter VI;

(v) where at any stage of a clinical trial, it comes to a conclusion that the trial is likely to compromise the right, safety or wellbeing of the trial subject, the committee may order discontinuation or suspension of the clinical trial and the same shall be intimated to the head of the institution conducting clinical trial and the Central Licencing Authority;

(vi) allow any officer authorised by the Central Licencing Authority to enter, with or without prior notice, to inspect the premises, any record, or any documents related to clinical trial, furnish information to any query raised by such authorised person, in relation to the conduct of clinical trial and to verify compliance with the requirements of these rules, Good Clinical Practices Guidelines and other applicable regulations for safeguarding the rights, safety and well-being of trial subjects;

(vii) comply with the requirements or conditions in addition to the requirements specified under the Act and these rules as may be specified by the Central Licencing Authority with the approval of the Central Government, to safeguard the rights of clinical trial subject or bioavailability or bioequivalence study subject.

12. Proceedings of Ethics Committee for clinical trial.— (1) No clinical trial or bioavailability or bioequivalence protocol and related documents shall be reviewed by an Ethics Committee unless at least five of its members as detailed below are present, namely:—

(i) medical scientist (preferably a pharmacologist);

(ii) clinician;

(iii) legal expert;

(iv) social scientist or representative of non-governmental voluntary agency or philosopher or ethicist or theologian or a similar person;

(v) lay person.

(2) The Ethics Committee may constitute one or more sub-committees of its members to assist in the functions assigned to it.

(3) The Ethics Committee may associate such experts who are not its members, in its deliberations but such experts shall not have voting rights, if any.

(4) Any change in the membership or the constitution of the registered Ethics Committee shall be intimated in writing to the Central Licencing Authority within thirty working days.

13. Maintenance of records by Ethics Committee for clinical trial.— (1) The Ethics Committee shall maintain data, record, registers and other documents related to the functioning and review of clinical trial or bioavailability study or bioequivalence study, as the case may be, for a period of five years after completion of such clinical trial.

(2) In particular and without prejudice to the generality of the sub-rule (1), the Ethics Committee shall maintain the following records for a period of five years after completion of every clinical trial or bioavailability study or bioequivalence study, namely:-

(i) the constitution and composition of the Ethics Committee;

(ii) the curriculum vitae of all members of the Ethics Committee;

(iii) standard operating procedures followed by the Ethics Committee;

(iv) national and international guidelines followed by the Ethics Committee;

(v) copies of the protocol, data collection formats, case report forms, investigators brochures, etc., submitted for review;

(vi) all correspondence with committee members and investigators regarding application, decision and follow up;

(vii) agenda of all Ethics Committee meetings and minutes of all Ethics Committee meetings with signature of the Chairperson;

(viii) copies of decisions communicated to applicants;

(ix) records relating to any order issued for premature termination of study with a summary of the reasons thereof;

(x) final report of the study including microfilms, compact disks or video recordings;

(xi) recommendation given by Ethics Committee for determination of compensation;

(xii) records relating to the serious adverse event, medical management of trial subjects and compensation paid.

(3) The Ethics Committee shall furnish the information maintained under sub-rule (1) and sub-rule (2), as and when required by the Central Licencing Authority or any other officer authorised on its behalf.

14. Suspension or cancellation of registration of Ethics Committee for clinical trial.— (1) Where Central Licencing Authority is of the opinion that any Ethics Committee fails to comply with any provision of the Act or these rules, it may issue show cause notice to such Ethics Committee specifying therein such non-compliances and the period within which reply shall be furnished by such Ethics Committee.

(2) On receipt of reply for the show cause notice within a period specified in the show cause notice, the Central Licencing Authority may give an opportunity of being heard, in person to such Ethics Committee.

(3) After consideration of the facts and reply given by the Ethics Committee under sub-rule (2), the Central Licencing Authority, may take one or more of the following actions, namely:-

(i) withdraw show cause notice issued under sub-rule(1);

(ii) issue warning to the Ethics Committee describing the deficiency or defect observed during inspection or otherwise, which may adversely affect the rights or well-being of the trial subject or the validity of clinical trial or bioavailability or bioequivalence study being conducted;

(iii) reject the results of clinical trial or bioavailability and bioequivalence study;

(iv) suspend for such period as considered appropriate or cancel the registration issued under rule 8;

(v) debar its members to oversee any clinical trial in future for such period as may be considered appropriate by the Central Licencing Authority.

(4) Where the Ethics Committee or any member of the Ethics Committee is aggrieved by an order of the Central Licencing Authority under sub-rule (3), such aggrieved Ethics Committee or member, may, within a period of sixty working days of the receipt of the order, file an appeal to the Central Government.

(5) Where an appeal has been filed under sub-rule (4), the Central Government may, after such enquiry, as it thinks necessary, and after giving an opportunity of being heard, pass such order in relation thereto as it thinks appropriate in the facts and circumstances of the case within a period of sixty working days from the date of filing of the appeal.

CHAPTER IV

ETHICS COMMITTEE FOR

BIOMEDICAL AND HEALTH RESEARCH

15. Ethics Committee for biomedical and health research.— Any institution or organisation which intends to conduct biomedical and health research shall be required to have an Ethics Committee to review and oversee the conduct of such research as detailed in National Ethical Guidelines for Biomedical and Health Research Involving Human Participants.

16. Constitution of Ethics Committee for biomedical and health research.— (1) The Ethics Committee referred to in rule 15, relating to biomedical and health research shall be constituted in accordance with the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants as may be specified by the Indian Council of Medical Research from time to time and shall function in accordance with said guidelines.

(2) The Ethics Committee referred to in sub-rule (1), shall review the work of the biomedical and health research centre before initiation and oversee throughout the duration of the biomedical and health research as per National Ethical Guidelines for Biomedical and Health Research Involving Human Participants.

(3) An institution or organisation or any person shall conduct any biomedical and health research with the approval of the Ethics Committee for biomedical and health research registered under rule 17.

(4) Any biomedical and health research shall be conducted in accordance with the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants as may be specified by the Indian Council of Medical Research from time to time.

(5) Institutions desirous of conducting biomedical and health research as well as clinical trials or bioavailability or bioequivalence study shall require obtaining registration from specified authorities as provided in rule 8 and rule 17.

17. Registration of Ethics Committee related to biomedical and health research.—

(1) An Ethics Committee constituted under rule 16, shall be required to register with the authority designated by the Central Government in the Ministry of Health and Family Welfare, Department of Health Research under these rules for which an application shall be made in Form CT-01 to the said authority.

(2) The application referred to in sub-rule (1) shall be accompanied with the information and documents as specified in Table 1 of the Third Schedule.

(3) On receipt of application in Form CT-01 under sub-rule (1), the authority designated under sub-rule (1) shall grant provisional registration which shall remain valid for a period of two years.

(4) After the grant of provisional registration under sub-rule (3), the authority designated under sub-rule (1) shall scrutinise the documents and information furnished with the application, and if satisfied that the requirements of these rules have been complied with, grant final registration to Ethics Committee in Form CT-03; or if not satisfied, reject the application, for reasons to be recorded in writing and the final registration in Form CT-03 shall supersede the provisional registration granted under sub-rule (3).

(5) An applicant who is aggrieved by the decision of the authority designated under sub-rule (1), may file an appeal within sixty working days from the date of receipt of such rejection before the Central Government in the Ministry of Health and Family Welfare, and the Central Government, may, after such enquiry as is considered necessary in the facts and circumstances of the case, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty working days.

(6) The Ethics Committee shall make an application for renewal of registration in Form CT-01 along with documents as specified in sub-rule (2) at least ninety days prior to the date of the expiry of its final registration:

Provided that if the application for renewal of registration is received by the authority designated under sub-rule (1), ninety days prior to the date of expiry, the registration shall continue to be in force until an order is passed by the said authority on the application:

Provided further that fresh set of documents shall not be required to be furnished, if there are no changes in such documents furnished at the time of grant of final registration, and if the applicant renders a certificate to that effect indicating that there is no change.

(7) The authority designated under sub-rule (1) shall after scrutiny of information furnished with the application and after such further enquiry, as considered necessary and on being satisfied that the requirements of these rules have been complied with, renew the registration of Ethics Committee in Form CT-03, or if not reject the application, for reasons to be recorded in writing.

(8) The authority shall take a decision under sub-rule (7) within a period of forty-five working days, from the date of application made under sub-rule(1).

(9) The registration granted in Form CT-03 shall remain valid for a period of five years from the date of its issue, unless suspended or cancelled by the authority designated under sub-rule (1).

(10) The function, proceedings of ethics committee and maintenance of records shall be as per the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants.

(11) In case there is a change in composition of registered Ethics Committee in an institution it shall be reported to the authority designated under sub-rule (1).

18. Suspension or cancellation of registration of Ethics Committee for biomedical and health research.— (1) Subject to provisions of rule 17, where the Ethics Committee fails to comply with any provision of these rules, the authority designated under sub-rule (1), may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, take one or more of the following actions, namely:—

(i) issue warning to the Ethics Committee describing the deficiency or defect observed, which may adversely affect the rights or well-being of the study subjects;

(ii) suspend for such period as considered appropriate or cancel the registration issued under rule 17;

(iii) debar its members to oversee any biomedical health research in future for such period as may be considered appropriate.

(2) Where the Ethics Committee or its member, as the case may be, is aggrieved by an order of the authority designated under sub-rule (1), it may, within a period of forty-five working days of the receipt of the order, make an appeal to the Central Government in the Ministry of Health and Family Welfare, and that Government may, after such enquiry, as deemed necessary, and after giving an opportunity of being heard, pass such order in relation thereto as may be considered appropriate in the facts and circumstances of the case.

CHAPTER V

CLINICAL TRIAL, BIOAVAILABILITY AND BIOEQUIVALENCE STUDY OF NEW DRUGS AND INVESTIGATIONAL NEW DRUGS

PART A

CLINICAL TRIAL

19. Clinical trial of new drug or investigational new drug.— (1) No person or institution or organisation shall conduct clinical trial of a new drug or investigational new drug,—

(i) except in accordance with the permission granted by the Central Licencing Authority; and

(ii) without the protocol there of having been approved by the Ethics Committee for clinical trial registered in accordance with the provisions of rule 8.

(2) Every person associated with the conduct of clinical trial of a new drug or investigational new drug shall follow the general principles and practices as specified in the First Schedule.

(3) No person or institution or organisation shall conduct clinical trial of a new drug or investigational new drug except in accordance with the procedure prescribed under the provisions of the Act and these rules.

20. Oversight of clinical trial site.— The work of every clinical trial site shall be overseen by an Ethics Committee for clinical trial registered under rule 8, before initiation and throughout the duration of the conduct of such trial.

21. Application for permission to conduct clinical trial of a new drug or investigational new drug.— (1) Any person or institution or organisation which intends to conduct clinical trial of a new drug or an investigational new drug shall make an application to the Central Licencing Authority duly filled in Form CT-04.

(2) The application made under sub-rule (1) shall be accompanied with the information and documents as specified in the Second Schedule and fee as specified in the Sixth Schedule:

Provided that no fee shall be payable for conduct of a clinical trial by a person of an institution or organisation funded or owned, wholly or partially by the Central Government or by a State Government.

22. Grant of permission to conduct clinical trial.— (1) The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application in Form CT-04 and such further enquiry, if any, as may be considered necessary,—

(i) if satisfied, that the requirements of these rules have been complied with, grant the permission to conduct clinical trial for a new drug or investigational new drug in Form CT-06;

(ii) in case, where the Central Licencing Authority considers that there are some deficiencies in the application and the same may be rectified, the said Authority shall inform the applicant about the deficiencies;

(iii) if not satisfied that the requirements of these rules have been complied with, reject the application, for the reasons to be recorded in writing.

(2) The decision under sub-rule (1) shall be taken within ninety working days.

(3) The applicant, after being informed, as referred to in clause (ii) of sub-rule (1), by the Central Licencing Authority, may,—

(i) rectify the deficiencies within a period specified by the Central Licencing Authority;

(ii) where the applicant rectifies the deficiency, as referred in sub-rule (1), and provides required information and documents, the Central Licencing Authority shall scrutinize the application again and if satisfied, grant permission to conduct clinical trial of the new drug or investigational new drug, or if not satisfied, reject the application within a period of ninety days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority, to reconsider the application within a period of sixty working days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and submission of required information and documents.

(4) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) or sub-rule (3), may file an appeal before the Central Government in the Ministry of Health and Family Welfare within forty-five days from the date of receipt of such decision and the that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty working days.

23. Permission to conduct clinical trial of a new drug or investigational new drug as part of discovery, research and manufacture in India.— (1) Notwithstanding anything contained in these rules, where any person or institution or organisation make an application under rule 21 to conduct clinical trial of a new drug or an investigational new drug which is complete as per these rules and fulfills the following conditions, namely:—

(i) the drug is discovered in India; or

(ii) research and development of the drug are being done in India and also the drug is proposed to be manufactured and marketed in India,

such application shall be disposed by way of grant of permission or rejection or processed by way of communication to rectify any deficiency of the application, as the case may be, as specified in rule 22, by the Central Licencing Authority within a period of thirty working days from the date of the receipt of the application by the said authority:

Provided that, where no communication has been received from the Central Licencing Authority to the applicant within the said period, the permission to conduct clinical trial shall be deemed to have been granted by the Central Licencing Authority and such permission shall be deemed to be legally valid for all purposes and the applicant shall be authorised to initiate clinical trial in accordance with these rules.

(2) The applicant who has taken deemed approval under the proviso to sub-rule (1) shall before initiating the clinical trial, inform the Central Licencing Authority in Form CT-4A and the Central Licencing Authority shall on the basis of the said information, take on record the Form CT-4A which shall become part of the official record and shall be called automatic approval of the Central Licencing Authority.

24. Permission to conduct clinical trial of a new drug already approved outside India.— Notwithstanding anything contained in these rules, where any person or institution or organisation makes an application under rule 21 to conduct clinical trial of a new drug which is already approved and marketed in a country, as specified under rule 101,the application, shall be disposed of by way of grant of permission or rejection or processed by way of communication to rectify any deficiency, as the case may be, as specified in rule 22, by the Central Licencing Authority within a period of ninety working days from the date of the receipt of the application by the said Authority.

25. Conditions of permission for conduct of clinical trial.— The permission granted by the Central Licencing Authority to conduct clinical trial under this Chapter shall be subject to following conditions, namely:—

(i) clinical trial at each site shall be initiated after approval of the clinical trial protocol and other related documents by the Ethics Committee of that site, registered with the Central Licencing Authority under rule 8;

(ii) where a clinical trial site does not have its own Ethics Committee, clinical trial at that site may be initiated after obtaining approval of the protocol from the Ethics Committee of another trial site; or an independent Ethics Committee for clinical trial constituted in accordance with the provisions of rule 7:

Provided that the approving Ethics Committee for clinical trial shall in such case be responsible for the study at the trial site or the centre, as the case may be:

Provided further that the approving Ethics Committee and the clinical trial site or the bioavailability and bioequivalence centre, as the case may be, shall be located within the same city or within a radius of 50 kms of the clinical trial site;

(iii) in case an ethics committee of a clinical trial site rejects the approval of the protocol, the details of the same shall be submitted to the Central Licensing Authority prior to seeking approval of another Ethics Committee for the protocol for conduct of the clinical trial at the same site;

(iv) the Central Licencing Authority shall be informed about the approval granted by the Ethics Committee within a period of fifteen working days of the grant of such approval;

(v) clinical trial shall be registered with the Clinical Trial Registry of India maintained by the Indian Council of Medical Research before enrolling the first subject for the trial;

(vi) clinical trial shall be conducted in accordance with the approved clinical trial protocol and other related documents and as per requirements of Good Clinical Practices Guidelines and the provisions of these rules;

(vii) status of enrolment of the trial subjects shall be submitted to the Central Licencing Authority on quarterly basis or as appropriate as per the duration of treatment in accordance with the approved clinical trial protocol, whichever is earlier;

(viii) six monthly status report of each clinical trial, as to whether it is ongoing, completed or terminated, shall be submitted to the Central Licencing Authority electronically in the SUGAM portal;

(ix) in case of termination of any clinical trial the detailed reasons for such termination shall be communicated to the Central Licencing Authority within thirty working days of such termination;

(x) any report of serious adverse event occurring during clinical trial to a subject of clinical trial, shall, after due analysis, be forwarded to the Central Licencing Authority, the chairperson of the Ethics Committee and the institute where the trial has been conducted within fourteen days of its occurrence as per Table 5 of the Third Schedule and in compliance with the procedures as specified in Chapter VI;

(xi) in case of injury during clinical trial to the subject of such trial, complete medical management and compensation shall be provided in accordance with Chapter VI and details of compensation provided in such cases shall be intimated to the Central Licencing Authority within thirty working days of the receipt of order issued by Central Licencing Authority in accordance with the provisions of the said Chapter;

(xii) in case of clinical trial related death or permanent disability of any subject of such trial during the trial, compensation shall be provided in accordance with Chapter VI and details of compensation provided in such cases shall be intimated to the Central Licencing Authority within thirty working days of receipt of the order issued by the Central Licencing Authority in accordance with the provisions of the said Chapter;

(xiii) the premises of the sponsor including his representatives and clinical trial sites, shall be open for inspection by officers of the Central Licencing Authority who may be accompanied by officers of the State Licencing Authority or outside experts as authorised by the Central Licencing Authority, to verify compliance of the requirements of these rules and Good Clinical Practices Guidelines, to inspect, search and seize any record, result, document, investigational product, related to clinical trial and furnish reply to query raised by the said officer in relation to clinical trial;

(xiv) where the new drug or investigational new drug is found to be useful in clinical development, the sponsor shall submit an application to the Central Licencing Authority for permission to import or manufacture for sale or for distribution of new drug in India, in accordance with Chapter X of these rules, unless otherwise justified;

(xv) the laboratory owned by any person or a company or any other legal entity and utilised by that person to whom permission for clinical trial has been granted used for research and development, shall be deemed to be registered with the Central Licensing Authority and may be used for test or analysis of any drug for and on behalf of Central Licensing Authority;

(xvi) the Central Licencing Authority may, if considered necessary, impose any other condition in writing with justification, in respect of specific clinical trials, regarding the objective, design, subject population, subject eligibility, assessment, conduct and treatment of such specific clinical trial;

(xvii) the sponsor and the investigator shall maintain the data integrity of the data generated during clinical trial.

26. Validity period of permission to initiate a clinical trial.— The permission to initiate clinical trial granted under rule 22 in Form CT-06 or automatic approval under rule 23 in Form CT 4A shall remain valid for a period of two years from the date of its issue, unless extended by the Central Licencing Authority.

27. Post-trial access of investigational new drug or new drug.— Where any investigator of a clinical trial of investigational new drug or new drug has recommended post-trial access of the said drug after completion of clinical trial to any trial subject and the same has been approved by the Ethics Committee for clinical trial, the post-trial access shall be provided by the sponsor of such clinical trial to the trial subject free of cost,—

(i) if the clinical trial is being conducted for an indication for which no alternative therapy is available and the investigational new drug or new drug has been found to be beneficial to the trial subject by the investigator; and

(ii) the trial subject or legal heir of such subject, as the case may be, has consented

in writing to use post-trial investigational new drug or new drug; and the investigator has certified and the trial subject or his legal heir, as the case may be, has declared in writing that the sponsor shall have no liability for post-trial use of investigational new drug or new drug.

28. Academic clinical trial.— (1) No permission for conducting an academic clinical trial shall be required for any drug from the Central Licencing Authority where,—

(i) the clinical trial in respect of the permitted drug formulation is intended solely for academic research purposes for a new indication or new route of administration or new dose or new dosage form; and

(ii) the clinical trial referred to in clause (i) has been initiated after prior approval by the Ethics Committee for clinical trial; and

(iii) the observations generated from such clinical trial are not required to be submitted to the Central Licencing Authority; and

(iv) the observations of such clinical trial are not used for promotional purposes.

(2) In the event of a possible overlap between the academic clinical trial and clinical trial or a doubt on the nature of study, the Ethics Committee concerned shall inform the Central Licencing Authority in writing indicating its views within thirty working days from the receipt of application to that effect.

(3) The Central Licencing Authority shall, after receiving the communication from the Ethics Committee referred to in sub-rule (2), examine it and issue necessary clarification, in writing, within thirty working days from the date of receipt of such communication:

Provided that where the Central Licencing Authority does not send the required communication to such Ethics Committee within thirty working days from the date of receipt of communication from the said Ethics Committee, it shall be presumed that no permission from the Central Licencing Authority is required.

(4) The approved academic clinical trial shall be conducted in accordance with the approved clinical trial protocol, ethical principles specified in National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, notified by the Indian Council of Medical Research with a view to ensuring protection of rights, safety and wellbeing of trial subject during conduct of clinical trial of licenced and approved drug or drug formulation for any new indication or new route of administration or new dose or new dosage form for academic research purposes.

29. Inspection of premises relating to clinical trial.— The person or the institution or the organisation permitted to conduct clinical trial under rule 22 in Form CT-06 or rule 23 in Form CT -4A including his representatives and investigator, shall allow any officer authorised by the Central Licencing Authority, who may, if considered necessary, be accompanied by an officer authorised by the State Licencing Authority, to enter the premises and clinical trial site with or without prior notice to inspect, search or seize, any record, statistical result, document, investigational drug and other related material; and reply to queries raised by the inspecting authority in relation to conduct of such clinical trial.

30. Suspension or cancellation of permission to conduct clinical trial.— (1) Where any person or institution or organisation to whom permission has been granted under rule 22 in Form CT-06 or rule 23 in Form CT-4A fails to comply with any provision of the Act and these rules, the Central Licencing Authority may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, take one or more of the following actions, namely:—

(i) issue warning in writing describing the deficiency or defect observed during inspection or otherwise, which may affect adversely the right, or well- being of a trial subject or the validity of clinical trial conducted;

(ii) reject the results of clinical trial;

(iii) suspend for such period as considered appropriate or cancel the permission granted under rule 22 in Form CT-06 or rule 23 in Form CT-4A;

(iv) debar the investigator or the sponsor including his representatives to conduct any clinical trial in future for such period as considered appropriate by the Central Licencing Authority.

(2) Where a person or an institution or an organisation to whom permission has been granted under rule 22 in Form CT-06 or rule 23 in Form CT-4A or the sponsor is aggrieved by the order of the Central Licencing Authority, the person or the institution or the organisation may, within a period of sixty working days of the receipt of the order, make an appeal

to the Central Government and that Government may, after such enquiry, as deemed necessary, and after affording an opportunity of being heard, pass such order in relation thereto as may be considered appropriate in the facts and circumstances of the case.

PART B

BIOAVAILABILITY AND BIOEQUIVALENCE STUDY

31. Bioavailability or bioequivalence study of new drug or investigational new drug.— (1) No bioavailability or bioequivalence study of any new drug or investigational new drug shall be conducted in human subjects by any person or institution or organisation except in accordance with the provisions of the Act and these rules.

(2) No person or institution or organisation shall conduct bioavailability or bioequivalence study of a new drug or investigational new drug in human subjects except in accordance with the permission granted by the Central Licencing Authority and without the protocol thereof having been approved by the Ethics Committee registered under rule 8.

(3) Every person associated with the conduct of bioavailability or bioequivalence study of a new drug or investigational new drug shall follow the general principles and practices as specified in the First Schedule.

32. Oversight of bioavailability or bioequivalence study centre.— The work of every bioavailability or bioequivalence study centre shall be overseen by an Ethics Committee registered under rule 8, before initiation and throughout the duration of the conduct of such study.

33. Application for permission to conduct bioavailability or bioequivalence study.— (1) Any person or institution or organisation which intends to conduct bioavailability or bioequivalence study of a new drug or an investigational new drug in human subjects shall obtain permission for conducting bioavailability or bioequivalence study from the Central Licencing Authority by making an application in Form CT-05.

(2) An application for grant of permission to conduct bioavailability or bioequivalence study of any new drug or investigational new drug shall be accompanied by a fee as specified in Sixth Schedule and such other information and documents as specified in the Table 2 of the Fourth Schedule:

Provided that no fee shall be payable for conducting a bioavailability or bioequivalence study by an institution or organisation owned or funded wholly and partially by the Central Government or a State Government.

34. Grant of permission to conduct bioavailability or bioequivalence study.— (1) The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application in Form CT-05 and such further enquiry, if any, as may be considered necessary,—

(i) if satisfied, that the requirements of these rules have been complied with, grant permission to conduct bioavailability or bioequivalence study for a new drug or investigational new drug in Form CT-07; or if not satisfied reject the application, for reasons to be recorded in writing within a period of ninety working days from the date of receipt of the application in Form CT-05;

(ii) in case, where the Central Licencing Authority considers that there are some deficiencies in the application and the same may be rectified, the said authority shall inform the applicant of the deficiencies within the stipulated period referred to in clause (i).

(2) The decision under sub-rule (1) shall be taken within ninety working days.

(3) The applicant, after being informed as referred to in clause (ii) of sub-rule (1) by the Central Licencing Authority, may,-

(i) rectify the deficiencies within a period specified by the Central Licencing Authority; and

(ii) where the applicant rectifies such deficiencies and provides required information and documents, the Central Licencing Authority shall scrutinise the application again and if satisfied, grant permission to conduct bioavailability or bioequivalence study of the new drug or investigational new drug; or if not satisfied, reject the application within a period of ninety working days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority, to reconsider the application within a period of sixty working days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and resubmission of required information and documents.

(4) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) and sub-rule (3), may file an appeal before the Central Government within forty-five working days from the date of receipt

of such decision and that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty working days.

35. Conditions of permission for conduct of bioavailability or bioequivalence study.— The permission granted by the Central Licencing Authority to conduct bioavailability or bioequivalence study under rule 34 shall be subject to following conditions, namely:—

(i) bioavailability or bioequivalence study at each site shall be initiated after approval of bioavailability or bioequivalence study protocol, as the case may be, and other related documents by the Ethics Committee of that site, registered under rule 8;

(ii) where a bioavailability or bioequivalence study centre does not have its own Ethics Committee, bioavailability or bioequivalence study at that site may be initiated after obtaining approval of the protocol from the Ethics Committee registered under rule 8:

Provided that the approving Ethics Committee shall in such case be responsible for the study at the centre:

Provided further that both the approving Ethics Committee and the centre, shall be located within the same city or within a radius of fifty kms of the bioavailability or bioequivalence study centre;

(iii) in case an Ethics Committee of a bioavailability or bioequivalence study centre rejects the approval of the protocol, the details of the same should be submitted to the Central Licensing Authority prior to seeking approval of another Ethics Committee for the protocol for conduct of the bioavailability or bioequivalence study at the same site;

(iv) the Central Licencing Authority shall be informed about the approval granted by the registered Ethics Committee within a period of 15 working days of the grant of such approval;

(v) bioavailability or bioequivalence study of new drug or investigational new drug shall be conducted only in the bioavailability or bioequivalence study centre registered with the Central Licencing Authority under rule 47;

(vi) bioavailability or bioequivalence study of investigational new drug shall be registered with the Clinical Trial Registry of India maintained by the Indian Council of Medical Research before enrolling the first subject for the study;

(vii) bioavailability or bioequivalence study shall be conducted in accordance with the approved bioavailability or bioequivalence study protocol and other related documents and as per requirements of Good Clinical Practices Guidelines and provisions of these rules;

(viii) in case of termination of any bioavailability or bioequivalence study, the detailed reasons for such termination shall be communicated to the Central Licencing Authority within thirty working days of such termination;

(ix) any report of serious adverse event occurring during bioavailability or bioequivalence study to a subject of such study, shall, after due analysis, be forwarded to the Central Licencing Authority, the chairperson of the Ethics Committee and the institute or the centre where the bioavailability or bioequivalence study, as the case may be, has been conducted within fourteen days of its occurrence as per Table 5 of the Third Schedule and in compliance with the procedures as specified in Chapter VI;

(x) in case of an injury during bioavailability or bioequivalence study to the subject of such study, complete medical management and compensation shall be provided in accordance with the provisions of Chapter VI and details of compensation provided in such cases shall be intimated to the Central Licencing Authority within thirty days of the receipt of order issued in accordance with the provisions of said Chapter;

(xi) in case of bioavailability or bioequivalence study related death or permanent disability of any subject of such study during the study, compensation shall be provided in accordance with Chapter VI and details of compensation provided in such cases shall be intimated to the Central Licencing Authority within thirty days of receipt of the order issued in accordance with the provisions of said Chapter;

(xii) the premises of the sponsor including his representatives and bioavailability and bioequivalence study centre shall be open for inspection by officers of the Central Licencing Authority who may be accompanied by officers of the State Licencing Authority or outside experts as authorised by the Central Licencing Authority, to verify compliance of the requirements of these rules and Good Clinical Practices Guidelines, to inspect, search and seize any record, result, document, investigational product, related to bioavailability or bioequivalence study, as the case may be, and

furnish reply to the queries raised by the said officer in relation to bioavailability or bioequivalence study;

(xiii) the bioavailability or bioequivalence study shall be initiated by enrolling the first subject within a period of one year from the date of grant of permission, failing which prior permission from the Central Licencing Authority shall be required.

36. Validity period of permission to conduct bioavailability or bioequivalence study.— (1) The permission to conduct bioavailability or bioequivalence study granted under rule 34 in Form CT-07 shall remain valid for a period of one year from the date of its issue, unless suspended or cancelled by the Central Licencing Authority.

(2) In exceptional circumstances, where the Central Licencing Authority is satisfied about the necessity for an extension beyond one year, the said authority may, on the request of the applicant made in writing, extend the period of permission granted for a further period of one year.

37. Inspection of premises relating to bioavailability or bioequivalence study.— The person or the institution or the organisation permitted to conduct bioavailability or bioequivalence study under rule 34 in Form CT-07 including his representatives and investigator, shall allow any officer authorised by the Central Licencing Authority, who may, if considered necessary, be accompanied by an officer authorised by the State Licencing Authority, to enter the premises and bioavailability or bioequivalence study centre with or without prior notice to inspect, search or seize, any record, statistical result, document, investigational drug and other related material and reply to the queries raised by the inspecting authority in relation to conduct of such bioavailability or bioequivalence study.

38. Suspension or cancellation of permission to conduct bioavailability or bioequivalence study.— (1) Where any person or institution or organisation to whom permission has been granted under rule 34 in Form CT-07 fails to comply with any provision of the Act and these rules, the Central Licencing Authority may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, take one or more of the following actions, namely:—

(i) issue warning in writing describing the deficiency or defect observed during inspection or otherwise, which may affect adversely the rights, or well- being of a subject enrolled in the study or the validity of bioavailability or bioequivalence study conducted;

(ii) reject the results of bioavailability or bioequivalence study, as the case may be;

(iii) suspend for such period as considered appropriate or cancel the permission granted under rule 34 in Form CT-07;

(iv) debar the investigator or the sponsor including his representatives, to conduct any bioavailability or bioequivalence study in future for such period as considered appropriate by the Central Licencing Authority.

(2) Where a person or an institution or an organisation to whom permission has been granted under rule 34 in Form CT-07or the sponsor is aggrieved by the order of the Central Licencing Authority, the person or the institution or the organisation may, within a period of sixty days of the receipt of the order, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary, and after affording an opportunity of being heard, pass such order in relation thereto as may be considered appropriate in the facts and circumstances of the case within a period of sixty days from the date of receipt of the appeal.

CHAPTER VI

COMPENSATION

39. Compensation in case of injury or death in clinical trial or bioavailability or bioequivalence study of new drug or investigational new drug.— (1) Where any death of a trial subject occurs during a clinical trial or bioavailability or bioequivalence study, the legal heir of the trial subject shall be provided financial compensation by the sponsor or its representative, who has obtained permission to conduct the clinical trial or bioavailability or bioequivalence study, in accordance with the procedure specified in rule 42.

(2) Where permanent disability or any other injury occurs to a trial subject during a clinical trial or bioavailability or bioequivalence study, the trial subject shall be provided financial compensation by the sponsor or its representative, who has obtained permission to conduct the clinical trial or bioavailability or bioequivalence study, in accordance with the procedure specified in rule 42.

(3) The financial compensation referred to in sub-rule (1) or sub-rule (2) shall be in addition to any expenses incurred on medical management of the trial subject.

(4) In the event of an injury, not being permanent in nature, the quantum of compensation shall be commensurate with the loss of wages of the subject as provided in the Seventh Schedule.

(5) The sponsor or its representative shall give an undertaking along with the application for clinical trial permission to the Central Licencing Authority to provide compensation in the case of clinical trial related injury or death for which subjects are entitled to compensation.

(6) Where the sponsor or its representative, who has obtained permission to conduct clinical trial or bioavailability or bioequivalence study, fails to provide financial compensation, as referred to in sub-rule (1) or sub-rule (2), the Central Licencing Authority shall, after affording an opportunity of being heard, by an order in writing, suspend or cancel the clinical trial or bioavailability or bioequivalence study or restrict the sponsor including its representative, who has obtained permission to conduct clinical trial or bioavailability or bioequivalence study, to conduct any further clinical trial or bioavailability or bioequivalence study or take any other action for such period as considered appropriate in the light of the facts and circumstances of the case.

40. Medical Management in clinical trial or bioavailability and bioequivalence study of new drug or investigational new drug.— (1) Where an injury occurs to any subject during clinical trial or bioavailability and bioequivalence study of a new drug or an investigational new drug, the sponsor, shall provide free medical management to such subject as long as required as per the opinion of investigator or till such time it is established that the injury is not related to the clinical trial or bioavailability or bioequivalence study, as the case may be, whichever is earlier.

(2) The responsibility for medical management as referred to in sub-rule (1), shall be discharged by the sponsor or the person who has obtained permission from the Central Licencing Authority.

(3) Where the sponsor or its representative, who has obtained permission to conduct clinical trial or bioavailability or bioequivalence study, fails to provide medical management, as referred to in sub-rule (1), the Central Licencing Authority shall after affording an opportunity of being heard, by an order in writing, suspend or cancel the clinical trial or bioavailability or bioequivalence study or restrict the sponsor including its representative, who has obtained permission to conduct clinical trial or bioavailability or bioequivalence study, to conduct any further clinical trial or bioavailability or bioequivalence study or take any other action for such period as considered appropriate in the light of the facts and circumstances of the case.

41. Consideration of injury or death or permanent disability to be related to clinical trial or bioavailability and bioequivalence study.— Any injury or death or permanent disability of a trial subject occurring during clinical trial or bioavailability or bioequivalence study due to any of the following reasons shall be considered as clinical trial or bioavailability or bioequivalence study related injury or death or permanent disability, namely:-

(a) adverse effect of the investigational product;

(b) violation of the approved protocol, scientific misconduct or negligence by the sponsor or his representative or the investigator leading to serious adverse event;

(c) failure of investigational product to provide intended therapeutic effect where, the required standard care or rescue medication, though available, was not provided to the subject as per clinical trial protocol;

(d) not providing the required standard care, though available to the subject as per clinical trial protocol in the placebo controlled trial;

(e) adverse effects due to concomitant medication excluding standard care, necessitated as part of the approved protocol;

(f) adverse effect on a child in-utero because of the participation of the parent in the clinical trial;

(g) any clinical trial procedures involved in the study leading to serious adverse event.

42. Procedure for compensation in case of injury or death during clinical trial, bioavailability and bioequivalence study.— (1) The investigator shall report all serious adverse events to the Central Licencing Authority, the sponsor or its representative, who has obtained permission from the Central Licencing Authority for conduct of clinical trial or bioavailability or bioequivalence study, as the case may be, and the Ethics Committee that accorded approval to the study protocol, within twenty-four hours of their occurrence; and if the investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reasons for delay to the satisfaction of the Central Licencing Authority along with the report of the serious adverse event.

(2) A case of serious adverse event of death shall be examined in the following manner, namely:-

(i) the Central Licencing Authority shall constitute an independent expert committee to examine the cases and make its recommendations to the said authority for arriving at the cause of death and quantum of compensation in case of clinical trial related death;

(ii) the sponsor or its representative and the investigator shall forward their reports on serious adverse event of death after due analysis to the Central Licencing Authority and the head of the institution where the clinical trial or bioavailability or bioequivalence study has been conducted within fourteen days of the knowledge of occurrence of serious adverse event of death;

(iii) the Ethics Committee for clinical trial shall forward its report on serious adverse event of death after due analysis along with its opinion on the financial compensation, if any, determined in accordance with the formula specified in the Seventh Schedule, to be paid by the said sponsor or its representative, who has obtained permission from the Central Licencing Authority for conduct of clinical trial or bioavailability or bioequivalence study, as the case may be, to the Central Licencing Authority within a period of thirty days of receiving the report of the serious adverse event of death from the investigator;

(iv) the Central Licencing Authority shall forward the report of the investigator, sponsor or its representative and the Ethics Committee to the Chairperson of the expert committee;

(v) the expert committee shall examine the report of serious adverse event of death and make its recommendations available to the Central Licencing Authority for the purpose of arriving at the cause of the serious adverse event of death within sixty days from the receipt of the report of the serious adverse event, and the expert committee while examining the event, may take into consideration, the reports of the investigator, sponsor or its representative and the Ethics Committee for clinical trial;

(vi) in case of clinical trial or the bioavailability or bioequivalence study related death, the expert committee shall also recommend the quantum of compensation, determined in accordance with the formula specified in the Seventh Schedule, to be paid by the sponsor or his representative who has obtained the permission to conduct the clinical trial or the bioavailability or bioequivalence study, as the case may be;

(vii) the Central Licencing Authority shall consider the recommendations of the expert committee and shall determine the cause of death with regards to the relatedness of the death to the clinical trial or the bioavailability or bioequivalence study, as the case may be;

(viii) in case of clinical trial or the bioavailability or bioequivalence study related death, the Central Licencing Authority shall, after considering the recommendations of the expert committee, by order, decide the quantum of compensation, determined as per the formula specified in the Seventh Schedule, to be paid by the sponsor or its representative and shall pass orders as deemed necessary within ninety days of the receipt of the report of the serious adverse event;

(ix) the sponsor or its representative shall pay the compensation in case the serious adverse event of death is related to clinical trial or the bioavailability or bioequivalence study, as specified in the order referred to in clause (viii) of the Central Licencing Authority within thirty days of the receipt of such order.

(3) Cases of serious adverse events of permanent disability or any other injury other than deaths shall be examined in the following manner, namely:—

(i) the sponsor or its representative, and the Investigator shall forward their reports on serious adverse event, after due analysis, to the Central Licencing Authority, chairperson of the Ethics Committee for clinical trial and head of the institution where the trial or bioavailability or bioequivalence study has been conducted within fourteen days of the reporting of serious adverse event;

(ii) the Ethics Committee for clinical trial shall forward its report on serious adverse event of permanent disability or any other injury other than deaths, as the case may be, after due analysis along with its opinion on the financial compensation, if any, determined in accordance with the formula specified in the Seventh Schedule, to be paid by the sponsor or its representative who has obtained permission to conduct clinical trial or the bioavailability or bioequivalence study, as the case may be, within thirty days of receiving the report of the serious adverse event;

(iii) the Central Licencing Authority shall determine the cause of the injury and pass order as specified in clause (iv), or may constitute an independent expert committee, wherever it considers necessary, to examine such serious adverse events of injury, and such independent expert committee shall recommend to the Central Licencing Authority for the purpose to arrive at the cause of the serious adverse event and also the quantum of compensation, as determined in accordance with formula as specified in the Seventh Schedule in case of clinical trial or bioavailability or bioequivalence study related injury, within a period of sixty days of receipt of the report of the serious adverse event;

(iv) in case of clinical trial or the bioavailability or bioequivalence study related injury, the Central Licencing Authority shall, by order, decide the quantum of compensation, determined in accordance with the formula specified in the Seventh Schedule, to be paid by the sponsor or his representative who has obtained the

permission to conduct the clinical trial or the bioavailability or bioequivalence study, as the case may be, within a period of ninety days of receipt of the report of the serious adverse event;

(v) the sponsor or its representative, who has obtained permission to conduct the clinical trial or bioavailability or bioequivalence study, as the case may be, shall pay the compensation in case of clinical trial or bioavailability or bioequivalence study related injury, as specified in the order of the Central Licencing Authority referred to in clause (iv) within thirty days of receipt of such order.

43. Medical management and compensation for injury or death relating to biomedical and health research overseen by an Ethics Committee for biomedical and health research as referred to in Chapter IV.— Notwithstanding anything contained in these rules, medical management and compensation for injury or death relating to biomedical and health research, overseen by an Ethics Committee for clinical trials as referred to in Chapter IV, shall be in accordance with the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants specified by the Indian Council of Medical Research from time to time.

CHAPTER VII

BIOAVAILABILITY AND BIOEQUIVALENCE STUDY CENTRE

44. Registration of bioavailability and bioequivalence study centre.— No bioavailability and bioequivalence study centre shall conduct any bioavailability study or bioequivalence study of a new drug or investigational new drug in human subjects except in accordance with the registration granted by the Central Licencing Authority under these rules.

45. Application for registration of bioavailability and bioequivalence study centre.— (1) Application for registration of any bioavailability and bioequivalence study centre with the Central Licencing Authority shall be made to the said authority in Form CT-08.

(2) The application under sub-rule (1) shall be accompanied by a fee as specified in the Sixth Schedule and such other information and documents as specified in the Fourth Schedule.

46. Inspection of bioavailability and bioequivalence study centre.— On receipt of an application under sub-rule (1) of rule 45, any officer authorised by the Central Licencing Authority who may be accompanied by the officers authorised by the State Licencing Authority, may cause an inspection of the bioavailability and bioequivalence study centre to verify the facility of the centre and the capacity of the applicant to comply with the requirements of these rules.

47. Grant of registration to bioavailability and bioequivalence study centre.— (1) The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application in Form CT-08 and such further enquiry, if any, as may be considered necessary, and if satisfied, that the requirements of these rules have been complied with, grant registration to the applicant in Form CT-09 within a period of ninety working days from the date of receipt of its application in Form CT-08; or if not satisfied, reject the application, for reasons to be recorded in writing, from the date the application was made under sub-rule (1) of rule 45;

(2) In case, where the Central Licencing Authority considers that there are some deficiencies in the application and the same are to be rectified, said authority shall inform the applicant of the deficiencies within the period as provided in sub-rule (1);

(3) The applicant may, after being informed by the Central Licencing Authority as specified in sub-rule(2),—

(i) rectify the deficiencies within a period specified by the Central Licencing Authority; and

(ii) where the applicant rectifies the deficiency within the period referred to in clause (i) and provides required information and documents, the Central Licencing Authority shall scrutinise the application again and if satisfied, grant registration to the applicant in Form CT-09 or if not satisfied, reject the application within a period of ninety days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority, to reconsider the application within a period of sixty days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and submission of required information and documents.

(4) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) or sub-rule (3), may file an appeal within forty-five days from the date of receipt of such rejection before the Central Government and that Government may, after such enquiry and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty days.

48. Validity period and renewal of registration of bioavailability and bioequivalence centre.— (1) The registration granted under rule 47 in Form CT-09 shall remain valid for a period of five years from the date of its issue, unless suspended or cancelled by the Central Licencing Authority.

(2)The bioavailability or bioequivalence centre shall make an application for renewal of registration in Form CT-08 along with documents as specified in the Fourth Schedule at least ninety days prior to date of expiry of its registration:

Provided that if the application for renewal of registration is received by the Central Licencing Authority ninety days prior to date of expiry, the registration shall continue to be in force until orders are passed by the said authority on the application.

(3)The Central Licencing Authority shall, after scrutiny of information enclosed with the application and after taking into account the inspection report, and such further enquiry, if any, as may be considered necessary, if satisfied, that the requirements of these rules,—

(i) have been complied with, grant registration or renew registration in Form CT-09;

(ii) have not been complied with, reject the application, for reasons to be recorded in writing, within a period of forty-five days, from the date the application was made under sub-rule (2).

49. Conditions of registration.— The registration granted under rule 47 in Form CT-09 shall be subject to following conditions, namely:—

(i) the centre shall maintain the facilities and adequately qualified and trained personnel as specified in the Fourth Schedule for performing its functions;

(ii) the centre shall initiate any bioavailability study or bioequivalence study of any new drug or investigational new drug in human subjects after approval of the protocol and other related documents by the Ethics Committee for clinical trial and permission of such study granted by the Central Licencing Authority;

(iii) where the bioavailability or bioequivalence study centre does not have its own Ethics Committee, bioavailability or bioequivalence study at that site may be initiated after obtaining approval of the protocol from another Ethics Committee for clinical trial registered under rule 8:

Provided that the approving Ethics Committee accepts the responsibility for the study at the centre and, both the approving Ethics Committee and the centre, are located within the same city or within a radius of fifty kms of the centre;

(iv) the Central Licencing Authority shall be informed about the approval of the Ethics Committee for clinical trial;

(v) bioavailability or bioequivalence study of investigational new drug shall be registered with the Clinical Trial Registry of India before enrolling the first subject for the study;

(vi) study shall be conducted in accordance with the approved protocol and other related documents and as per requirements of Good Clinical Practices Guidelines and provisions of the Act and these rules;

(vii) in case of termination of any such study prematurely, the detailed reasons for such termination shall be communicated to the Central Licencing Authority immediately;

(viii) any report of serious adverse event occurring during study to the subject of such study shall, after due analysis, be forwarded to Central Licencing Authority within fourteen days of its occurrence in the format as specified in Table 5 of the Third Schedule and in compliance with the procedures as specified in rule 42;

(ix) in case of an injury to the study subject during study, the complete medical management and compensation in the case of study related injury shall be provided in accordance with the provisions of Chapter VI and details of compensation paid to the trial subject in such cases shall be intimated to the Central Licencing Authority within thirty days of receipt of the order;

(x) in case of death, permanent disability, injury other than death and permanent disability, as the case may be, of a study subject, compensation shall be provided in accordance with the provisions of Chapter VI and details of compensation paid to the trial subject or his legal heir, as the case may be, in such cases shall be intimated to the Central Licencing Authority within thirty days of receipt of the order;

(xi) if there is any change in constitution or ownership of the bioavailability and bioequivalence study centre, the centre shall intimate about the change in writing to the Central Licencing Authority within thirty days of such change;

(xii) the study centre shall maintain data, records, and other documents related to the conduct of the bioavailability or bioequivalence study for a period of five years after completion of such study or for at least two years after the expiration date of the batch of the new drug or investigational new drug studied, whichever is later;

(xiii) the bioavailability and bioequivalence study centre shall allow any officer authorized by the Central Licencing Authority who may be accompanied by an officer authorised by State Licencing Authority to enter the premises with or without prior notice, to inspect any record, statistical observation or results or any documents related to bioavailability study and bio-equivalence study and furnish information to the queries raised by such authorised person, in relation to the conduct of the said study;

(xiv) the Central Licencing Authority may, if considered necessary, impose additional condition, in writing with justification, in respect of specific bioavailability and bioequivalence study regarding the objective, design, subject population, subject eligibility, assessments, conduct and treatment of such specific study.

50. Inspection of bioequivalence and bioavailability study centre registered with Central Licencing Authority.— The bioavailability and bioequivalence study centre registered by the Central Licencing Authority under Rule 47 in Form CT-09, including his representatives and investigator, shall allow any officer authorised by the Central Licencing Authority, who may be accompanied by an officer authorised by the State Licencing Authority, to enter the premises of the bioavailability and bioequivalence study centre with or without prior consent, to inspect, search or seize, any record, document, investigational product and other related material and reply to queries raised by the inspecting authority in relation to functioning of the centre.

51. Suspension or cancellation of registration of bioavailability and bioequivalence study centre.— (1) Where any bioavailability and bioequivalence study centre including his representatives or investigator, fails to comply with any provision of the Act and these rules, the Central Licencing Authority may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, take one or more of the following actions, namely:—

(a) issue warning in writing describing the deficiency or defect observed during inspection or otherwise, which may affect adversely the right or well-being of trial subject or the validity of any study conducted;

(b) reject the results of the study;

(c) suspend the conduct of a study;

(d) suspend for such period as considered appropriate or cancel the registration granted under rule 47 in Form CT-09; and

(e) debar the centre including its representatives to conduct any bioavailability and bioequivalence study in future for such period as considered appropriate by the Central Licencing Authority.

(2) Where a bioavailability and bioequivalence study centre registered under Form CT-

09 against whom an order has been made under sub-rule (1) is aggrieved by the order of the Central Licencing Authority, the bioavailability and bioequivalence study centre may within a period of sixty days of the receipt of the order, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary and after affording an opportunity of being heard, pass such orders in relation thereto as may be considered appropriate in the facts and circumstances of the case.

CHAPTER VIII

MANUFACTURE OF NEW DRUGS OR INVESTIGATIONAL NEW DRUGS FOR CLINICAL TRIAL, BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

52. Application for permission to manufacture of new drug or investigational new drug for clinical trial or bioavailability and bioequivalence study or for examination, test and analysis. –

(1) No person shall manufacture a new drug or an investigational new drug to conduct clinical trial or bioavailability or bioequivalence study or for examination, test and analysis without obtaining permission to manufacture such new drug or investigational new drug from the Central Licencing Authority.

(2) Any person who intends to manufacture a new drug or an investigational new drug to conduct clinical trial or bioavailability and bioequivalence study or for examination, test and analysis shall make an application in Form CT-10 to the Central Licencing Authority to obtain the permission referred to in sub-rule(1).

(3) The application referred in sub-rule (2) shall be accompanied with such documents and information as specified in the Fourth Schedule along with fee as specified in the Sixth Schedule.

53. Grant of permission to manufacture new drugs or investigational new drugs for clinical trial or bioavailability or bioequivalence study, or for examination, test and analysis.— (1)The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application in Form CT-10 and such further enquiry, if any, as may be considered necessary, if satisfied, that the requirements of these rules have been complied with, grant permission to manufacture the new drug or investigational new drug for conduct of clinical trial or bioavailability or bioequivalence study or for examination, test and analysis, as the case may be, the new drug or investigational new drug, in Form CT-11 within a period of ninety working days from the date of receipt of its application in Form CT-10; or if not satisfied that the requirements of these rules have been complied with, reject the application, for reasons to be recorded in writing, within a period of ninety working days from the date the application was made under sub-rule (2) of rule 52.

(2)In case, where the Central Licencing Authority considers that there are some deficiencies in the application and the same may be rectified, the said authority shall inform the applicant of the deficiencies within the period specified in sub-rule (1)

(3) The applicant may, after being informed by the Central Licencing Authority as specified in sub-rule (2),—

(i) rectify the deficiencies within a period specified by the Central Licencing Authority; and

(ii) where the applicant rectifies the deficiency within the period referred to in clause (i) and provides required information and documents, the Central Licencing Authority shall scrutinise the application again and if satisfied, grant permission to manufacture for conduct of clinical trial or bioavailability or bioequivalence study, or for examination, test and analysis, as the case may be, for the new drug or investigational new drug; or if not satisfied, reject the application within a period of ninety working days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority to reconsider the application within a period of sixty working days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and submission of required information and documents.

(4) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) or sub-rule (3), may file an appeal before the Central Government within forty-five days from the date of receipt of such decision and that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty days from the date of filing the appeal.

54. Validity period of permission to manufacture of new drug or investigational new drugs for clinical trial or bioavailability and bioequivalence study, or for examination, test and analysis.— (1) The permission granted under rule 53 in Form CT-11 shall remain valid for a period of three years from the date of its issue, unless suspended or cancelled by the Central Licencing Authority.

(2) In exceptional circumstances, where the Central Licencing Authority is satisfied about the necessity and exigency, it may, on the request of the applicant made in writing, by order, and for reasons to be recorded, extend the period of the permission granted for a further period of one year.

55. Condition of permission.— The grant of permission under rule 53 in Form CT-11 shall be subject to the following conditions, namely:—

(i) the permission holder shall make use of new drug manufactured under Form CT-11 only for the purposes of conducting clinical trial or bioavailability and bioequivalence study or for examination, test and analysis and no part of it shall be sold in the market or supplied to any other person or agency or institution or organisation;

(ii) the permission holder shall manufacture new drugs for the purposes of clinical trial or bioavailability and bioequivalence study or for examination, test and analysis in small quantities in accordance with the provisions of these rules and at places specified in the permission and in accordance with the principles of Good Manufacturing Practices;

(iii) the permission holder shall keep a record of new drugs manufactured and persons to whom the drugs have been supplied for clinical trial or bioavailability and bioequivalence study or for examination, test and analysis;

(iv) where new drug manufactured for purposes of clinical trial or bioavailability or bioequivalence study or for examination, test and analysis is left over or remains unused or gets damaged or its specified shelf life has expired or has been found to be of sub- standard quality, the same shall be destroyed and action taken in respect thereof shall be recorded.

56. Licence to manufacture new drugs or investigational new drugs for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis under the Drugs and Cosmetics Rules, 1945.— (1) After obtaining permission under rule 53, the person, who intends to manufacture the new drug or investigational new drugs for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis of new drugs or investigational new drugs, shall make an application for grant of licence to manufacture new drug or investigational new drugs in accordance with the provisions of the Act and the Drugs and Cosmetics Rules, 1945.

(2) The application referred in sub-rule (1) shall be accompanied by the permission under rule 53 in Form CT-11 obtained by the applicant from the Central Licencing Authority to manufacture the new drugs for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis.

57. Inspection of new drugs or investigational new drugs manufactured for clinical trial or bioavailability and bioequivalence study or for examination, test and analysis.— The permission holder or the person, to whom new drugs have been supplied for conducting clinical trial or bioavailability and bioequivalence study or for examination, test and analysis, shall allow any officer authorised by the Central Licencing Authority or the State Licencing Authority to enter, the premises where the new drug is being manufactured or stored, with or without prior notice, to inspect such premises and records, investigate the manner in which the drugs are being manufactured or stored or used and to take sample thereof.

58. Suspension or cancellation of manufacturing permission for new drug or investigational new drugs.— (1) Subject to provisions of rule 55, where the permission holder, fails to comply with any provision of the Act and these rules, the Central Licencing Authority may, after giving that person an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, take one or more of the following actions, namely:—

(i) suspend the permission for such period as considered appropriate;

(ii) cancel the permission granted under rule 53 in Form CT-11.

(2) Where the permission holder whose permission has been suspended or cancelled under sub-rule (1) is aggrieved by an order of the Central Licencing Authority, he may, within sixty days of the receipt of the order, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary and after affording an opportunity of being heard, pass such order in relation thereto as may be considered appropriate in the facts and circumstances of the case.

59. Application for permission to manufacture unapproved active pharmaceutical ingredient for development of pharmaceutical formulation for test or analysis or clinical trial or bioavailability and bioequivalence study.—

(1) Where a manufacturer of a pharmaceutical formulation intends to procure active pharmaceutical ingredient, which is not approved under rule 76 or rule 81, for development of formulation and to manufacture batches for test or analysis or clinical trial or bioavailability and bioequivalence study of such formulation, the application for permission to manufacture such drug shall be made to the Central Licencing Authority by the manufacturer of pharmaceutical formulation in Form CT-12 and manufacturer of the active pharmaceutical ingredient in Form CT-13**.**

(2) The application under sub-rule (1) shall be accompanied by such other particulars and documents as are specified in Form CT-12 or Form CT-13, as the case maybe.

60. Grant of permission to manufacture unapproved active pharmaceutical ingredient for development of pharmaceutical formulation for test or analysis or clinical trial or bioavailability and bioequivalence study.— (1) The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application under rule 59 in Form CT-12 or CT-13, as the case may be, and such further enquiry, if any, as may be considered necessary:—

(i) if satisfied, that the requirements of these rules have been complied with, grant the permission to the manufacturer of active pharmaceutical ingredient in Form CT-15 to manufacture the unapproved active pharmaceutical ingredient and to the manufacturer of pharmaceutical formulation in Form CT-14 for development of pharmaceutical formulation for test or analysis or clinical trial or bioavailability and bioequivalence study within ninety working days; or

(ii) if not satisfied that the requirements of these rules have been complied with, reject the application, for reasons to be recorded in writing, within a period of ninety working days, from the date, the application was made under sub-rule (1) of rule 59; or

(iii) if the Central Licencing Authority considers that there are some deficiencies in the application and the same may be rectified, the said Authority shall inform the applicant of the deficiencies within the stipulated period referred to in clause (i).

(2) The applicant may, after being informed, by the Central Licencing Authority as referred to in clause (iii) of sub-rule (1),-

(i) rectify the deficiencies within a period specified by the Central Licencing Authority;

(ii) where the applicant rectifies the deficiency, as referred in sub-rule (1), within the period referred to in clause (i) and provides required information and documents, the Central Licencing Authority shall scrutinise the application again and if satisfied, grant permission to the manufacturer of active pharmaceutical ingredient in Form CT-15 to manufacture the unapproved active pharmaceutical ingredient and to the manufacturer of pharmaceutical formulation in Form CT-14 for development of pharmaceutical formulation for test or analysis or clinical trial or bioavailability and bioequivalence study; or if not satisfied, reject the application within a period of ninety working days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority, to reconsider the application within a period of sixty days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and submission of required information and documents.

(3) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) or sub-rule (2), may file an appeal before the Central Government within sixty days from the date of receipt of such rejection and that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty days from the date of filing the appeal.

61. Validity period of the permission to manufacture unapproved active pharmaceutical ingredient and its formulation for test or analysis or clinical trial or bioavailability and bioequivalence study.— (1) The permission granted under rule 60 in Form CT-14 or Form CT-15, as the case may be, shall remain valid for a period of three years from the date of its issue, unless suspended or cancelled by the Central Licencing Authority.

(2) In exceptional circumstances, where the Central Licencing Authority is satisfied about the necessity and exigency, it may, on the request of the applicant made in writing, by order and for reasons to be recorded extend the period of permission granted for a further period of one year.

62. Suspension or cancellation of permission to manufacture unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or bioavailability and bioequivalence study.— (1) Subject to provision of rule 60, where the formulation manufacturer or an active pharmaceutical ingredient manufacturer fails to comply with any provisions of the Act and these rules, the Central Licencing Authority may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, take one or more of the following actions, namely:—

(i) suspend the permission for such period as considered appropriate;

(ii) cancel the permission granted under rule 60 in Form CT-14 or Form CT-15.

(2) Where the formulation manufacturer or active pharmaceutical ingredient manufacturer whose permission has been suspended or cancelled under sub-rule (1), is aggrieved by an order of the Central Licencing Authority, such manufacturer may, within forty-five days of the receipt of the order, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary and after affording an opportunity of being heard, pass such orders in relation thereto as may be considered appropriate in the facts and circumstances of the case.

63. Conditions of permission.— The permission granted under rule 60 in Form CT-14 or Form CT-15 shall be subject to following conditions, namely:—

(i) the manufacturer of pharmaceutical formulation or the active pharmaceutical ingredient shall make use of the unapproved active pharmaceutical ingredient manufactured on the basis of permission issued under rule 60, only for the purposes specified in the said permission, and no part of it shall be sold in the market;

(ii) the permission holder shall manufacture such active pharmaceutical ingredient or its pharmaceutical formulation for the purposes as specified in permission in accordance with the provisions of these rules and at places referred to in such permission and, in case, the manufacture of such drugs is for clinical trial or bioavailability and bioequivalence study, it should be manufactured in accordance with the principles of Good Manufacturing Practices;

(iii) the manufacturer of a pharmaceutical formulation and active pharmaceutical ingredient referred to in clause (i), shall keep all necessary records to indicate the quantity of drug procured, manufactured, used, disposed of in any manner and other matters related thereto;

(iv) where unapproved active pharmaceutical ingredient and pharmaceutical formulation manufactured in accordance with the permission issued under rule 60 is left over or remains, unused or gets damaged or its shelf life has expired or has been found to be of sub-standard quality, the same shall be destroyed and action taken in respect thereof shall be recorded.

64. Licence to manufacture unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or bioavailability and bioequivalence study under the Drugs and Cosmetics Rules, 1945.— (1) After obtaining permission under rule 60, the person intending to manufacture unapproved active pharmaceutical ingredient or pharmaceutical formulation of the new drug or investigational new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis, shall make an application for grant of licence to manufacture unapproved active pharmaceutical ingredient or pharmaceutical formulation for test or analysis or clinical trial or bioavailability in accordance with the provisions of the Act and the Drugs and Cosmetics Rules, 1945.

(2) The application referred in sub-rule (1) shall be accompanied by the permission granted under rule 60 in Form CT-14 or Form CT-15, as the case may be, obtained by the applicant from the Central Licencing Authority to manufacture unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or bioavailability or bioequivalence study.

65. Inspection of manufacturer of unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or bioavailability and bioequivalence study.— The manufacturer of active pharmaceutical ingredient or formulation, referred to in rule 60, shall allow any officer authorised by the Central Licencing Authority or the person authorised by the State Licencing Authority to enter the premises where the unapproved active pharmaceutical ingredient is being manufactured, stored and used, with or without prior notice, to inspect such premises and records, inspect the manner in which the unapproved active pharmaceutical ingredient is being manufactured and stored or used and to take sample thereof.

66. Manner of labelling.— (1) Any new drug or investigational new drug manufactured, for the purpose of clinical trial or bioavailability or bioequivalence study, shall be kept in containers bearing labels, indicating the name of the drug or code number, batch or lot number, wherever applicable, date of manufacture, use before date, storage conditions, name of the institution or organisation or the centre where the clinical trial or bioavailability or bioequivalence study is proposed to be conducted, name and address of the manufacturer, and the purpose for which it has been manufactured.

(2) Where a new drug or an investigational new drug is manufactured by the permission holder on behalf of another person, the permission holder shall indicate on the label of the container of such drug, the name and address of the manufacturer and the person to whom it is being supplied along with the scientific name of such drug, if known, or the reference which shall enable such drug to be identified and the purpose for which it is manufactured.

(3) No person or manufacturer shall alter, obliterate or deface any inscription or mark made on the container, label or wrapper of any new drug manufactured without permission of the Central Licencing Authority.

CHAPTER IX

IMPORT OF NEW DRUGS AND INVESTIGATIONAL NEW DRUGS FOR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALANCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

67. Application for import of new drug or investigational new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis.— (1) No person shall import a new drug or any substance relating thereto for conducting clinical trial or bioavailability or bioequivalence study or for examination, test and analysis except in accordance with the licence granted by Central Licencing Authority.

(2) Any person or institution or organisation who intends to import a new drug or any substance relating thereto for conducting clinical trial or bioavailability or bioequivalence study or for examination, test and analysis shall make an application in Form CT-16 to the Central Licencing Authority.

(3) The application under sub-rule (2) shall be accompanied by a fees specified in the Sixth Schedule and such other information and documents as specified in Form CT-16.

68. Grant of licence for import of new drug or investigational new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis.— (1) The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application in Form CT-16 and such further enquiry, if any, as may be considered necessary,—

(i) if satisfied, that the requirements of these rules have been complied with, grant the licence to import of new drug or investigational new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis in Form CT-17 within a period of ninety days from the date of receipt of its application in FormCT-16;

(ii) in case, where the Central Licencing Authority considers that there are some deficiencies in the application and the same may be rectified, the said Authority shall inform the applicant of the deficiencies within the stipulated period referred to in clause (i);

(iii) if not satisfied that the requirements of these rules have been complied with, reject the application, for reasons to be recorded in writing, within a period of ninety days, from the date of the application made under sub-rule (2) of rule 67;

(2) The applicant may, after being informed, by the Central Licencing Authority as referred to in clause (ii) of sub-rule (1),—

(i) rectify the deficiencies within a period specified by the Central Licencing Authority;

(ii) where the applicant rectifies the deficiency, as referred in clause (i) and provides required information and documents, the Central Licencing Authority shall scrutinise the application again and if satisfied, grant licence to import of new drug or investigational new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis; or if not satisfied, reject the application within a period of ninety working days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority, to reconsider the application within a period of sixty days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and submission of required information and documents.

(3) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) or sub-rule (2), may file an appeal before the Central Government within sixty days from the date of receipt of such rejection and that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty working days.

69. Validity period of licence for import of new drugs for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis.— (1) The licence granted under rule 68 in Form CT-17 shall remain valid for a period of three years from the date of its issue, unless suspended or cancelled by the Central Licencing Authority.

(2) In exceptional circumstances, where the Central Licencing Authority is satisfied about the necessity and exigency, it may, on the request of the applicant made in writing, extend the period of the licence granted under rule 68 for a further period of one year.

70. Condition of licence.— The licence granted under rule 68 in Form CT-17 is subject to the following conditions, namely:—

(i) it shall be the responsibility of the licencee to ensure that the new drug has been manufactured in accordance with the provisions of the Act, these rules and principles of Good Manufacturing Practices;

(ii) the licencee shall make use of a new drug or substance relating thereto imported on the basis of licence granted under rule 68 in Form CT-17 only for the purposes of clinical trial or bioavailability or bioequivalence study or for examination, test and analysis and no part of such new drug or substance relating thereto shall be sold in the market or supplied to any other person or agency or institution or organisation;

(iii) the licencee shall maintain records of imported new drug or substance relating thereto to indicate the quantity of drug imported, used, disposed of in any manner and other matters related thereto;

(iv) where the imported new drug or substance relating thereto is left over or remains unused or gets damaged or its specified shelf life has expired or has been found to be of sub-standard quality, the same shall be destroyed and details of action taken in such cases shall be recorded.

71. Inspection of imported new drug for clinical trial or the bioavailability or bioequivalence study or for examination, test and analysis.— The person licenced to import a new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis shall allow any officer authorised by the Central Licencing Authority to enter the premises where a new drug or substances relating thereto has been manufactured or imported, is stocked or is being used, with or without prior notice, to inspect such premises and records, investigate the manner in which such drug is being stocked or used or to take sample thereof if so required by the Central Licencing Authority or his authorised person.

72. Suspension or cancellation of import licence of new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis.— (1) Where the person to whom a licence has been granted under rule 68, fails to comply with any provisions of the Act and these rules, the Central Licencing Authority may, after giving an opportunity to show cause and after affording an opportunity of being heard, by an order in writing, suspend or cancel the licence for such period as considered appropriate either wholly or in respect of some of the substances to which the violation relates and direct the imported new drugs to be disposed of in the manner specified in the said order.

(2) Where the person whose licence has been suspended or cancelled under sub-rule (1), is aggrieved by an order of the Central Licencing Authority, such person may, within a period of forty-five days of the receipt of the order of suspension or cancellation, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary and after affording an opportunity of being heard, pass such order in relation thereto as considered appropriate within a period of sixty working days from the date of filing the appeal.

73. Manner of labelling.— (1) Any new drugs or investigational new drugs imported for the purpose of clinical trial or bioavailability or bioequivalence study or for examination, test and analysis shall be kept in containers bearing labels, indicating the name of the drug or code number, batch or lot number, wherever applicable, date of manufacture, use before date, storage conditions, name of the institution or organisation or the centre where the clinical trial or bioavailability or bioequivalence study or for examination, test and analysis is proposed to be conducted, name and address of the manufacturer, and the purpose for which it has been imported.

(2) Where a new drug or an investigational new drug is imported by the licencee on behalf of another person, the licencee shall indicate on the label of the container of the such drug, the name and address of the importer and the person to whom it is being supplied along with the scientific name of such drug, if known, or the reference which shall enable such drug to be identified and the purpose for which it is manufactured.

(3) No person or importer shall alter, obliterate or deface any inscription or mark made on the container, label or wrapper of any new drug imported without permission of the Central Licencing Authority.

CHAPTER X

IMPORT OR MANUFACTURE OF NEW DRUG FOR SALE OR FOR DISTRIBUTION

74. Regulation of new drug.— No person shall import or manufacture for sale or for distribution any new drug in the form of active pharmaceutical ingredient or pharmaceutical formulation, as the case may be, except in accordance with the provisions of the Act and these rules.

75. Application for permission to import new drug for sale or distribution.— (1) Any person who intends to import new drug in the form of active pharmaceutical ingredient or pharmaceutical formulation, as the case may be, for sale or for distribution in India, shall make an application to obtain a permission from the Central Licencing Authority in Form CT-18 along with a fee as specified in the Sixth Schedule:

Provided that an application for grant of permission to import a new drug, in the form of active pharmaceutical ingredient which is a new drug not approved earlier, shall be accompanied by an application for grant of permission to manufacture pharmaceutical formulation of that new drug.

(2) Where a new drug proposed to be marketed by any person is a new drug having unapproved new molecule, the application in Form CT-18 shall be accompanied by data and other particulars including result of local clinical trial as specified in the Second Schedule along with data specified in Table 1 of the Second Schedule and accompanied with fee as specified in the Sixth Schedule.

(3) Where a new drug is proposed to be marketed which has been approved as a new drug in the country, the application in Form CT-18 shall be accompanied by data and other particulars as specified in the Second Schedule along with data specified in Table 2 of the Second Schedule and accompanied with fee as specified in the Sixth Schedule.

(4) Where a new drug which is already permitted for certain claims, is now proposed to be marketed by any person for new claims, new indication or new dosage form or new route of administration or new strength, application in Form CT-18 shall be accompanied by data and other particulars including result of local clinical trial as specified in the Second Schedule along with data specified in Table 3 of the Second Schedule and accompanied with fee as specified in the Sixth Schedule.

(5) In case a new drug which is a fixed dose combination, the application in CT-18 shall be accompanied by data and other particulars including result of local clinical trial as the case may be, as specified in the Second Schedule along with data specified in Table 1 or Table 2 or Table 3, as the case may be, of the Second Schedule and accompanied with fee as specified in the Sixth Schedule.

(6) A person intends to market phyto-pharmaceutical drugs shall make an application in CT-18 to the Central Licencing Authority along with data specified in Table 4 of the Second Schedule and it shall be accompanied with a fee as specified in the Sixth Schedule.

(7) The local clinical trial may not be required to be submitted along with the application referred to in sub-rule (1) if,—

(i) the new drug is approved and marketed in countries specified by the Central Licencing Authority under rule 101 and if no major unexpected serious adverse events have been reported; or

(ii) the application is for import of a new drug for which the Central Licencing Authority had already granted permission to conduct a global clinical trial which is ongoing in India and in the meantime such new drug has been approved for marketing in a country specified under rule 101; and

(iii) there is no probability or evidence, on the basis of existing knowledge, of difference in Indian population of the enzymes or gene involved in the metabolism of the new drug or any factor affecting pharmacokinetics and pharmacodynamics, safety and efficacy of the new drug; and

(iv) the applicant has given an undertaking in writing to conduct Phase IV clinical trial to establish safety and effectiveness of such new drug as per design approved by the Central Licencing Authority:

Provided that the Central Licencing Authority may relax this condition, where the drug is indicated in life threatening or serious diseases or diseases of special relevance to Indian health scenario or for a condition which is unmet need in India such as XDR tuberculosis, hepatitis C, H1N1, dengue, malaria, HIV, or for the rare diseases for which drugs are not available or available at a high cost or if it is an orphan drug.

(8) The submission of requirements relating to animal toxicology, reproduction studies, teratogenic studies, perinatal studies, mutagenicity and carcinogenicity in the application referred to in sub-rule (1), may be modified or relaxed in case of new drugs approved and marketed for more than two years in other countries, if the Central Licencing Authority is satisfied that there is adequate published evidence regarding the safety of the drug, subject to other provisions of these rules.

76. Grant of permission for import of new drugs for sale or distribution.— (1) The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application in Form CT-18 and such further enquiry, if any, as may be considered necessary,—

(i) if satisfied, that the requirements of these rules have been complied with, grant the permission to import new drug, in the form of active pharmaceutical ingredient for sale or for distribution in Form CT-19 or pharmaceutical formulation for sale or for distribution in Form CT-20, as the case may be, within a period of ninety working days from the date of receipt of its application in Form CT-18;

(ii) in case, where the Central Licencing Authority considers that there are some deficiencies in the application and the same may be rectified, said Authority shall inform the applicant of the deficiencies within the stipulated period referred to in clause (i);

(iii) if not satisfied that the requirements of these rules have been complied with, reject the application, for that reasons to be recorded in writing, within a period of ninety working days, from the date of the application made under rule 75.

(2) The applicant may, after being informed by the Central Licencing Authority as referred to in clause (ii) of sub-rule (1),—

(i) rectify the deficiencies within a period specified by the Central Licencing Authority;

(ii) where the applicant rectifies the deficiency, as referred in clause (i), within the period referred to in clause (i) and provides required information and documents, the Central Licencing Authority shall scrutinise the application again and if satisfied, grant permission to import new drug, in the form of active pharmaceutical ingredient for sale or for distribution in Form CT-19 or pharmaceutical formulation for sale or for distribution in Form CT-20, as the case may be; or if not satisfied, reject the application within a period of ninety days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority, to reconsider the application within a period of sixty days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and submission of required information and documents.

(3) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) and sub-rule (2), may file an appeal before the Central Government within sixty days from the date of receipt of such rejection and that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty working days from the date of filing the appeal.

77. Condition of permission for import of new drugs for sale or distribution.— The permission for import of new drugs for sale or for distribution under rule 76 shall be subject to the following conditions, namely:—

(i) the new drugs shall conform to the specifications approved by the Central Licencing Authority;

(ii) the labeling of the drugs shall conform to the requirements specified in the Drugs and Cosmetics Rules, 1945;

(iii) the label on the immediate container of the drug as well as the packing in which the container is enclosed should contain the following warning: "WARNING: To be sold by retail on the prescription of a ……only" which shall be in red box;

(iv) as post marketing surveillance, the applicant shall submit Periodic Safety Update Reports as specified in the Fifth Schedule;

(v) all reported adverse reactions related to drug shall be intimated to the Central Licencing Authority and regulatory action resulting from their review shall be complied with;

(vi) no claims except those mentioned above shall be made for the drug without prior approval of the Central Licencing Authority;

(vii) specimen of the carton, labels, package insert that will be adopted for marketing the drug in the country shall be got approved from the Central Licencing Authority before the drugs is marketed;

(viii) in case of import, each consignment shall be accompanied by a test or analysis report;

(ix) if long-term stability data submitted do not cover the proposed shelf-life of the product, the stability study shall be continued to firmly establish the shelf-life and the complete stability data shall be submitted.

78. Suspension or cancellation of import permission for new drug.— (1) Where the importer fails to comply with any provision of the Act and these Rules, the Central Licencing Authority may, after giving show cause notice and an opportunity of being heard, by an order in writing, may suspend the permission for such period as considered appropriate or cancel the permission.

(2) Where the importer whose permission has been suspended or cancelled under sub-rule (1), is aggrieved by an order of the Central Licencing Authority, such importer may, within forty-five days of the receipt of the order, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary and after giving an opportunity of being heard, pass such order as may be considered appropriate in the facts and circumstances of the case.

79. Licence to import new drug for sale or for distribution under the Drugs and Cosmetics Rules, 1945.— (1) After obtaining permission under Rule 76, the person intending to import new drug for sale shall make an application to the Central Licencing Authority as per provisions of the Drugs and Cosmetics Rules, 1945 to obtain a licence for import of new drug for sale or for distribution.

(2) The application referred in sub-rule (1) shall be accompanied by the permission in Form CT-19 or Form CT-20, as the case may be, obtained by the applicant from the Central Licencing Authority to import the new drugs.

80. Application for permission to manufacture new drug for sale or distribution.— (1) A person who intends to manufacture new drug in the form of active pharmaceutical ingredient or pharmaceutical formulation, as the case may be, for sale or distribution, shall make an application for grant of permission to the Central Licencing Authority in Form CT-21 along with a fee as specified in the Sixth Schedule:

Provided that no fee shall be required to be paid along with the application for manufacture of a new drug based on successful completion of clinical trials from Phase I to Phase III under these Rules in India, where fee has already been paid by the same applicant for conduct of such clinical trials:

Provided further that an application for grant of permission to manufacture a new drug for sale or distribution in the form of active pharmaceutical ingredient having a new drug molecule not approved earlier shall be accompanied by an application for grant of permission to manufacture for sale or distribution of pharmaceutical formulation of the said new drug.

(2) Where a new drug, proposed to be manufactured, is a new drug having unapproved new molecule, the application in Form CT-21 shall be accompanied by data and other particulars including results of local clinical trial as specified in the Second Schedule along with data specified in Table 1 of the Second Schedule and accompanied with fee as specified in the Sixth Schedule.

(3) Where a new drug, proposed to be manufactured which has been approved as a new drug, the application in Form CT-21 shall be accompanied by data and other particulars as specified in the Second Schedule

along with data specified in Table 2 of the Second Schedule and accompanied with fee as specified in Sixth Schedule.

(4) Where a new drug which is already permitted for certain claims, is now proposed to be manufactured for new claims, namely new indication or new dosage form or new route of administration or new strength, application in Form CT-21 shall be accompanied by data and other particulars including results of local clinical trial as specified in the Second Schedule along with data specified in Table 3 of the Second Schedule and accompanied with fee as specified in the Sixth Schedule.

(5) In case of a new drug which is a fixed dose combination, the application in Form CT-21 shall be accompanied by data and other particulars including results of local clinical trial as specified in the Second Schedule along with data specified in Table 1 or Table 2 or Table 3, as the case may be, of the Second Schedule and accompanied with fee as specified in the Sixth Schedule.

(6) A person who intends to market phyto -pharmaceutical drugs shall make an application in Form CT-21 to the Central Licencing Authority along with data specified in Table 4 of Second Schedule and it shall be accompanied with a fee as specified in the Sixth Schedule.

(7) The local clinical trial may not be required to be submitted along with the application referred to in sub-rule (1) if,-

(i) the new drug is approved and marketed in countries specified by the Central Licencing Authority under rule101 and if no major unexpected serious adverse events have been reported; or

(ii) there is no probability or evidence, on the basis of existing knowledge, of difference in Indian population of the enzymes or gene involved in the metabolism of the new drug or any factor affecting pharmacokinetics and pharmacodynamics, safety and efficacy of the new drug; and

(iii) the applicant has given an undertaking in writing to conduct Phase IV clinical trial to establish safety and effectiveness of such new drug as per design approved by the Central Licencing Authority:

Provided that the Central Licencing Authority may relax this condition, where the drug is indicated in life threatening or serious diseases or diseases of special relevance to Indian health scenario or for a condition which is unmet need in India such as XDR tuberculosis, hepatitis C, H1N1, dengue, malaria, HIV, or for the rare diseases for which drugs are not available or available at a high cost or if it is an orphan drug.

(8) In the application referred to in sub-rule (1), the submission of requirements relating to animal toxicology, reproduction studies, teratogenic studies, perinatal studies, mutagenicity and carcinogenicity may be modified or relaxed in case of new drugs approved and marketed for several years in other countries, if the Central Licencing Authority is satisfied that there is adequate published evidence regarding the safety of the drug, subject to other provisions of these rules.

81. Grant of permission for manufacture of new drug for sale or distribution.— (1) The Central Licencing Authority may, after scrutiny of the information and documents furnished with the application in Form CT-21 and such further enquiry, if any, as may be considered necessary,—

(i) if satisfied, that the requirements of these rules have been complied with, grant permission to manufacture new drug, in the form of active pharmaceutical ingredient for sale or for distribution in Form CT-22 or pharmaceutical formulation for sale or for distribution in Form CT-23, as the case may be, within a period of ninety working days from the date of receipt of its application in Form CT-21;

(ii) if not satisfied that the requirements of these rules have been complied with, reject the application, for reasons to be recorded in writing, within a period of ninety working days, from the date, the application made under rule 80; and

(iii) in case, where the Central Licencing Authority considers that there are some deficiencies in the application and the same may be rectified, said Authority shall inform the applicant of the deficiencies within the stipulated period referred to in clause (i).

(2) The applicant may, after being informed by the Central Licencing Authority as referred to in clause (iii) of sub-rule (1),—

(i) rectify the deficiencies within a period specified by the Central Licencing Authority;

(ii) where the applicant rectifies the deficiency within the period referred to in clause (i) and provides required information and documents, the Central Licencing Authority shall scrutinise the application again and if satisfied, grant permission to manufacture new drug, in the form of active pharmaceutical ingredient for sale or for distribution in Form CT-22 or pharmaceutical formulation for sale or for

distribution in Form CT-23, as the case may be; or if not satisfied, reject the application within a period of ninety working days reckoned from the day when the required information and documents were provided:

Provided that in case of rejection, the applicant may request the Central Licencing Authority, to reconsider the application within a period of sixty working days from the date of rejection of the application on payment of fee as specified in the Sixth Schedule and submission of required information and documents.

(3) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1) or sub-rule (2), may file an appeal before the central Government within sixty days from the date of receipt of such rejection and that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty working days from the date of filing the appeal.

82. Condition of permission for manufacture of new drugs for sale or distribution.— The permission granted under rule 81 in Form CT-22 or in Form CT-23 shall be subject to following conditions, namely:—

(i) the new drugs shall conform to the specifications approved by the Central Licencing Authority;

(ii) the labeling of the drugs shall conform to the requirements specified in the Drugs and Cosmetics Rules, 1945;

(iii) the label on the immediate container of the drug as well as the packing in which the container is enclosed should contain the following warning:

"WARNING: To be sold by retail on the prescription of a_____ Only" and it shall be in box with red back ground.

(iv) as post marketing surveillance, the applicant shall submit Periodic Safety Update Reports as specified in the Fifth Schedule;

(v) all reported serious unexpected adverse reactions related to the drug shall be intimated to the Central Licencing Authority and regulatory action resulting from their review shall be complied with;

(vi) no claims except those mentioned above shall be made for the drug without prior approval of the Central Licencing Authority;

(vii) specimen of the carton, labels, package insert that will be adopted for marketing the drug in the country shall be got approved from the Central Licencing Authority before the drugs is marketed;

(viii) if long-term stability data submitted do not cover the proposed shelf-life of the product, the stability study shall be continued to firmly establish the shelf-life and the complete stability data shall be submitted.

83. Licence to manufacture a new drug for sale or for distribution under Drugs and Cosmetics Rules, 1945.— (1) After obtaining permission granted under rule 81, the person intending to manufacture a new drug for sale shall make an application for grant of licence to manufacture for sale or for distribution in accordance with the provisions of the Act and the Drugs and Cosmetics Rules, 1945.

(2) The application referred in sub-rule (1) shall be accompanied by the permission in Form CT-22 or Form CT-23, as the case may be, obtained by the applicant from the Central Licencing Authority to manufacture the new drug.

84. Suspension or cancellation of permission.— (1) Where the manufacturer fails to comply with any provisions of the Act, these rules and any condition of the permission, the Central Licencing Authority may, after affording an opportunity of being heard, suspend or cancel the permission for such period as considered appropriate either wholly or in respect of some of the substances to which the violation relates.

(2) Where the manufacturer whose permission has been suspended or cancelled under sub-rule (1) is aggrieved by an order of the Central Licencing Authority, such manufacturer may, within thirty days of the receipt of the order, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary and after affording an opportunity of being heard, pass such orders in relation thereto as considered appropriate.

85. Responsibility of importers or manufacturers in marketing of new drugs.— The manufacturer or importer of new drugs shall be responsible for marketing a new drug for the approved indication and in only such dosage form for which it has been permitted:

Provided that the manufacturer or importer of new drug shall not be punished for the consequences resulting from use of the drug for an indication other than for which the drug has been approved where the manufacturer proves that he has not been involved in any manner in the promotion of use of the new drug for other than approved indication.

CHAPTER XI

IMPORT OR MANUFACTURE OF UNAPPROVED NEW DRUG FOR TREATMENT OF PATIENTS IN GOVERNMENT HOSPITAL AND GOVERNMENT MEDICAL INSTITUTION

86. Application for import of unapproved new drug by Government hospital and Government medical institution.— (1) Notwithstanding anything contained in these rules, a medical officer of a Government hospital or a Government medical institution, may import new drug, which has not been permitted in the country under Chapter X of these rules, but approved for marketing in the country of origin for treatment of a patient suffering from life threatening disease or disease causing serious permanent disability or disease requiring therapies for unmet medical needs, by making an application duly certified by the Medical Superintendent of the Government hospital or Head of the Government medical institution, as the case may be, to the Central Licencing Authority in Form CT-24.

(2) The application under sub-rule (1) shall be accompanied by such other particulars and documents as are specified in Form CT-24 along with fee as specified in the Sixth Schedule.

87. Grant of licence for import of unapproved new drug by Government hospital and medical institution.— (1)The Central Licencing Authority, after scrutiny of information and documents enclosed with the application and such further enquiry, if any, as considered necessary, may,—

(i) if satisfied, that the requirements of these rules have been complied with, grant licence for import of an unapproved new drug by Government hospital and Government medical institution in Form CT-25;

(ii) if not satisfied with the requirements as referred to in sub-clause (i), reject the application, for reasons to be recorded in writing, within a period of ninety days, from the date of application made under sub-rule (1) of rule 86.

(2) An applicant who is aggrieved by the decision of the Central Licencing Authority under sub-rule (1), may file an appeal before the Central Government within forty-five days from the date of receipt of such rejection and that Government, may, after such enquiry, and after giving an opportunity of being heard to the appellant, dispose of the appeal within a period of sixty working days from the date of filing the appeal.

(3) The quantity of any single drug imported on the basis of licence granted under sub-rule (1), shall not exceed one hundred average dosages per patient but in exceptional circumstances and on being satisfied about the necessity and exigency the Central Licencing Authority may allow import of unapproved new drugs in larger quantities depending on the condition and requirement of such patient.

88. Conditions of licence.— The import licence granted under rule 87 in Form CT-25 shall be subject to the following conditions, namely:—

(i) the licence shall remain valid for a period of three years from the date it has been issued;

(ii) the licence shall be displayed in the premises of the medical institution including where the unapproved new drug is being stocked and used in the office of the Medical Superintendent of the Government hospital or Head of Government medical institution;

(iii) the licencee shall stock the unapproved new drug imported under this licence under proper storage conditions;

(iv) the unapproved new drug imported under this licence shall be exclusively used for treatment of the patient and supplied under the supervision of a registered pharmacist and no part of such unapproved new drug shall be sold in the market or supplied to any other person, agency, institution or place;

(v) the registered pharmacist shall maintain a record as specified in Annexure of Form CT-25, countersigned by the Medical Superintendent of the Government hospital or Head of the Government medical institution which shall be produced, on demand by the officer authorised by the Central Licencing Authority under these rules;

(vi) the Government hospital and Government medical institution referred to in sub-rule (1) of rule 87, shall submit to the Central Licencing Authority a half yearly report about the status and stock of unapproved new drugs imported, utilised and destroyed;

(vii) where the unapproved new drugs imported under licence granted under sub-rule (1) of rule 87, are left over or remain unused or get damaged or its specified shelf life has expired or has been found to be of sub-standard quality, the same shall be destroyed and the action taken in respect thereof be recorded as referred to in clause(iv) by the registered pharmacist.

89. Suspension or cancellation of import licence for unapproved new drug of Government hospital or Government medical institution.— (1) Where any licencee referred to rule 87, fails to comply with any provision of the Act and these rules, the Central Licencing Authority, may after affording an opportunity of being heard, by an order in writing, suspend or cancel the permission for such period as considered appropriate either wholly or in respect of some of the substances to which the violation relates.

(2) Where the licencee, whose licence has been suspended or cancelled under sub-rule (1) is aggrieved by an order of the Central Licencing Authority, he may, within a period of forty-five days from the receipt of the order, make an appeal to the Central Government and that Government may, after such enquiry, as deemed necessary and after affording an opportunity of being heard, pass such orders in relation thereto as considered appropriate.

90. Inspection of unapproved new drug imported by Government hospital or Government medical institution.— The licencee referred in rule 87, shall allow any person authorised by the Central Licencing Authority who may be accompanied by an officer authorised by the State Licencing Authority, to enter the premises where the unapproved new drugs are stored and is being used, with or without prior notice, and records, to inspect such premises, store and record, investigate the manner in which the drugs are being used and stocked and to take sample thereof.

91. Application for permission to manufacture unapproved new drug but under clinical trial, for treatment of patient of life threatening disease.— (1) Where any medical officer of a Government hospital or Government medical institution prescribes in special circumstances any new drug for a patient suffering from serious or life threatening disease for which there is no satisfactory therapy available in the country and which is not yet approved by the Central Licencing Authority but the same is under clinical trial in the country, then, such new drug may be approved to be manufactured in limited quantity subject to provisions of these rules.

(2) Where any manufacturer intends to manufacture new drug referred to in sub-rule (1), he shall obtain the consent in writing from the patient to whom the unapproved new drug has been prescribed under sub-rule (1) or his legal heirs and make an application to the Ethics Committee of the Government hospital or medical institution, as the case may be for obtaining its specific recommendation for manufacture of such unapproved new drug.

(3) After obtaining the recommendation of the Ethics Committee under sub-rule (2), the manufacturer shall make an application in Form CT-26 to obtain the permission to the Central Licencing Authority for manufacturing specific new drug.

(4) The application under sub-rule (3) shall be accompanied by consent in writing from the patient referred to in sub-rule (1) or his legal heirs regarding use of such unapproved new drug and such other particulars and documents as are specified in Form CT-26 along with fee as specified in the Sixth Schedule.

92. Grant of permission to manufacture unapproved new drug but under clinical trial, for treatment of patient of life threatening disease.— (1) The Central Licencing Authority may, after scrutiny of information and documents enclosed with the application and such further enquiry, if any, as considered necessary,-

(i) if satisfied, that the requirements of these rules have been complied with, grant permission to manufacture unapproved new drug but under clinical trial for treatment of patient of serious or life threatening disease in Form CT-27;

(ii) if not satisfied with the requirements as referred to in clause (i), reject the application, for reasons to be recorded in writing, within a period of ninety days, from the date of application made under rule 91.

(2) The quantity of any single new drug manufactured on the basis of permission granted under sub-rule (1) shall not exceed one hundred average dosages per patient but in exceptional circumstances on the basis of the prescription of the medical officer referred to in sub-rule (1) and the recommendation of the Ethics Committee, the Central Licencing Authority may allow the manufacture of such new drug in larger quantity.

93. Condition of permission.— The permission granted under rule 92 in Form CT-27, is subject to the following conditions, namely:-

(i) the permission shall remain valid for a period of one year from the date it has been issued;

(ii) the patient to whom the unapproved new drug is prescribed under sub-rule (1) of rule 92 shall use such unapproved new drug under the supervision of the medical officer at the place specified in the permission or at such other places, as the Central Licencing Authority may authorise;

(iii) the manufacturer to whom the permission is granted under sub-rule (1) of rule 92, shall make use of the unapproved new drug only for the purposes specified in the permission and no part of it shall be sold in the market or supplied to any other person, agency, institution or place;

(iv) the manufacturer referred to in clause (iii) shall keep record of the unapproved new drugs manufactured, stored and supplied by him to the patient in a register in the format as specified in annexure of Form CT-27;

(v) the manufacturer referred to in clause (iii), shall submit to the Central Licencing Authority a half yearly report about the status of the unapproved new drugs manufactured, supplied to the authorised patient;

(vi) the manufactured unapproved new drugs shall be kept and stored in accordance with the storage conditions specified on its label and supplied to the patient under the supervision of the medical officer referred to in sub-rule (1) of rule 91 or a registered pharmacist duly authorised by him;

(vii) the registered pharmacist shall maintain a record of the full name and address of the patients, diagnosis, dosage schedule, total quantity of drugs received and issued, countersigned by the Medical Superintendent of the Government hospital or Head of the medical institution which shall be produced, on demand by the officer authorised by the Central Licencing Authority under the Act;

(viii) where the unapproved new drug manufactured in accordance with the permission issued under sub-rule (1) of rule 92, is left over or remain unused or get damaged or its specified shelf life has expired or has been found to be of sub-standard quality, the same shall be destroyed by the manufacturer and the action taken in respect thereof shall be recorded;

(ix) the permission holder shall inform the Central Licencing Authority of the occurrence of any serious adverse event and action taken thereon including any recall within fifteen days of occurrence of such event.

94. Inspection of unapproved new drug but under clinical trial manufactured for patient of life threatening disease.— The manufacturer referred to in rule 92, shall allow persons authorised by the Central Licencing Authority including the person authorised by the State Licencing Authority to enter the premises where the unapproved new drug is being manufactured, stored and supplied, with or without prior notice, to inspect such premises and records, investigate the manner in which the unapproved new drug is being manufactured, supplied and to take sample thereof.

95. Suspension or cancellation of permission to manufacture unapproved new drug but under clinical trial.— (1) Where the manufacturer to whom permission is granted under rule 92 fails to comply with any provision of the Act and these rules, the Central Licencing Authority, may, after giving an opportunity of being heard, by an order, in writing, suspend or cancel the permission for such period as considered appropriate either wholly or in respect of some of the substances to which the violation relates.

(2) Where the manufacturer whose permission is suspended or cancelled under sub-rule (1) is aggrieved by an order of the Central Licencing Authority, he may, within a period of forty-five days from the receipt of the order, make an appeal to the Central Government in respect of suspension or cancellation of the permission and that Government, may, after such enquiry, as deemed necessary and after affording an opportunity of being heard, pass such orders in relation thereto as considered appropriate.

96. Licence to manufacture an unapproved new drug but under clinical trial, for treatment of patient of life threatening disease under the Drugs and Cosmetics Rules, 1945.— (1) After obtaining permission under rule 92, the person intending to manufacture an unapproved new drug, which is under clinical trial, for treatment of patient of serious or life threatening disease, shall make an application for grant of licence to manufacture the unapproved new drug under the provisions of the Act and the Drugs and Cosmetics Rules, 1945.

(2) The application referred in sub-rule (1) shall be accompanied by the permission in Form CT-27 obtained by the applicant from the Central Licencing Authority to import the new drugs.

CHAPTER XII

AMENDEMENTS OF DRUGS AND COSMETICS RULES, 1945

97. In the Drugs and Cosmetics Rules 1945, after rule 122DA the following new rule shall be inserted, namely:—

"122DAA. Non-application of certain rules for new drugs and investigational new drugs for human use.— Part XA and Schedule Y shall not be applicable in respect of new drugs and investigational new drugs for human use from the date of coming into force of the New Drugs and Clinical Trials Rules, 2019, and the references in respect of human use made in the these rules shall respectively be omitted, and the construction thereof shall be construed accordingly and shall stand amended with all cogent meaning of the grammar".

CHAPTER XIII

MISCELLANEOUS

98. Pre-submission meeting.— (1) Any person who intends to make an application for grant of licence or permission for import or manufacture of new drugs or to conduct clinical trial may, request by making an application in writing, for a pre-submission meeting with the Central Licencing Authority or any other officer authorised by the Central Licencing Authority for seeking guidance about the requirements of law and procedure of such licence or permission of manufacturing process, clinical trial and other requirements.

(2) The application for pre-submission meeting under sub-rule (1) may be accompanied by particulars and documents referred to in the Second Schedule, as available with the applicant to support his proposal along with fee as specified in the Sixth Schedule.

(3) Where the applicant intends to seek guidance about the sale process of new drugs or import licence, in addition to the purposes referred to in sub-rule (2), the fee as specified in the Sixth Schedule shall be submitted along with the application.

(4) Where the Central Licencing Authority is satisfied that the application is incomplete or the information or the documents submitted along with the same are inadequate, he may within a period of thirty days from the receipt of the same intimate the facts to the applicant in writing and direct him to furnish such further information or documents as are necessary in accordance with the provisions of the Act and these rules.

(5) In the pre-submission meeting, the Central Licencing Authority or any other person authorised by it shall provide suitable clarification to the applicant.

99. Post-submission meeting.— (1) If the applicant desires to seek clarification in person in respect of pending application and queries related thereto, the applicant may make an application for a post-submission meeting with the officer designated by the Central Licencing Authority within a period of fifteen days from the date the query was received for seeking guidance with regards to the queries concerning pending application.

(2) The applicant shall clearly state the points on which clarification is required and after receipt of such application, the designated officer shall inform the time and date scheduled for post submission meeting.

(3) The summary of the clarification provided by the designated officer shall be made available to the applicant.

(4) The application for post-submission meeting under sub-rule (1) shall be accompanied with the fee as specified in the Sixth Schedule.

(5) In the post submission meeting, the officer designated by the Central Licencing Authority shall provide suitable clarification to the applicant.

100. Constitution of expert committee or group of experts by Central Licencing Authority.— The Central Licencing Authority may, when so required, constitute one or more expert committee or group of experts with specialisation in relevant fields, with the approval of Central Government, to evaluate scientific and technical matters relating to drugs and such committee or group may, give its recommendations to that authority on matters referred to it within a period of sixty days from the date of reference.

101. Name of countries for purpose of new drug approval.— The Central Licencing Authority, with the approval of the Central Government, may specify, by an order, the name of the countries, from time to time, for considering

waiver of local clinical trial for approval of new drugs under Chapter X and for grant of permission for conduct of clinical trial under Chapter V.

102. Mode of payment of fee.— The fees prescribed under these rules, in case of application made to the Central Licencing Authority, shall be paid through challan or by electronic mode, in the Bank of Baroda, Kasturba Gandhi Marg, New Delhi-110001 or any other branch of Bank of Baroda, or any other bank, notified by the Ministry of Health and Family Welfare in the Central Government, to be credited under the Head of Account "0210- Medical and Public Health, 04-Public Health, 104-Fees and Fines.

103. Debarment of applicant.— (1) Whoever himself or, any other person on his behalf, or applicant is found to be guilty of submitting misleading, or fake, or fabricated documents, may, after giving him an opportunity to show cause as to why such an order should not be made, in writing, stating the reasons thereof, be debarred by the Central Licencing Authority for such period as deemed fit.

(2) Where an applicant is aggrieved by an order made by the Central Licencing Authority under sub-rule (1), such applicant may, within thirty days from the receipt of the order, make an appeal to that Government and that Government, may, after such enquiry as it considers necessary, and after affording an opportunity of being heard, pass such orders as considered appropriate.

104. Order of suspension or revocation in public domain.— In case, the Central Licencing Authority issue any order of suspension or revocation or cancellation of any permission or licence or registration granted under these rules, such order shall be made available in the public domain immediately by uploading it in the website of Central Drugs Standard Control Organisation.

105. Digitalisation of Forms.— The forms prescribed under these rules may be suitably modified for conversion into digital forms by the Central Drugs Standard Control Organisation and such modification shall not require any amendment in these rules.

106. Applicability in case of inconsistency.— If there is any inconsistency between these rules and any other rule made under the Act, the provisions of these rules shall prevail over such other rules.

107. Savings.— (1) Notwithstanding the non-applicability of the Drugs and Cosmetics Rules, 1945, the approvals or permissions or licences or certificates issued under the provisions of the Act and the said rules in respect of new drugs and investigational new drugs for human use, prior to commencement of these rules, shall be deemed to be valid till its expiry under the corresponding provisions of said rules;

(2) Any things done or any action taken or purported to have been done or taken, including any rule, notification, inspection, order or notice made or issued or any appointment or declaration made or any operation undertaken or any direction given or any proceedings taken or any penalty, punishment, forfeiture or fine imposed under the Drugs and Cosmetics Rules, 1945 shall, be deemed to have been done or taken under the corresponding provisions of these rules and shall always remain valid for all purposes.

FIRST SCHEDULE

(*See rules 19 and 31*)

GENERAL PRINCIPLES AND PRACTICES FOR CLINICAL TRIAL

1. General Principles.— (1) The principles and guidelines for protection of trial subjects as described in Third Schedule as well as Good Clinical Practices guidelines shall be followed in conduct of any clinical trial.

(2) The sponsor and investigator share the responsibilities for the protection of trial subject together with ethics committee. The responsibilities of sponsor, investigator and ethics committee are described in the Third Schedule.

(3) The results of non-clinical studies or previous clinical trials should be sufficient to ensure that the new drugs or investigational new drug is safe for the proposed clinical trial.

(4) Throughout the clinical trial and drug development process, the animal toxicological data and clinical data generated should be evaluated to ensure their impact for the safety of the trial subject.

2. Approach in design and analysis.— (1) Clinical trial should be planned, designed, conducted, analysed and reported according to sound scientific and ethical principles. Following important principles should be followed:

(a) The primary objective of any clinical trial should be clearly and explicitly stated which may include exploratory or confirmatory characterisation of safety, efficacy, assessment of pharmacokinetic and pharmacodynamic parameters;

(b) The clinical trial should be designed appropriately so that it provides the desired information;

(c) Appropriate comparator may be utilised to achieve the objective with respect to primary and secondary end points. Comparison may be made with placebo, no treatment, active controls or of different doses of the new drug or investigational new drug;

(d) The number of subjects to be included in the clinical trial should be adequate depending on the nature and objective of the clinical trial.

3. Development Methodology: (1) Non clinical studies,-

(a) The nature of non-clinical studies and their timing in respect of conduct of clinical trial should be determined taking following aspects in to consideration:

(i) characteristics of the new drug or investigational new drug;

(ii) disease of conditions for which the new drug or investigational new drug is intended to be indicated;

(iii) duration and exposure in clinical trial subject;

(iv) route of administration.

(b) The detailed requirements of non-clinical studies have been specified in the Second Schedule.

(c) For first in human studies the dose should be calculated carefully based on the non-clinical pharmacological, toxicological data generated.

(2) Phases in Clinical Trial: Clinical drug development generally consists of four phases (Phase I-IV). The details of these phases are described as under.

(a) Phase I.— The objective of studies in this phase is the estimation of safety and tolerability with the initial administration of an investigational new drug into humans. Studies in this phase of development usually have non-therapeutic objectives and may be conducted in healthy subjects or certain types of patients. Drugs with significant potential toxicity e.g. cytotoxic drugs are usually studied in patients. Phase I trial should preferably be carried out by investigators trained in clinical pharmacology with access to the necessary facilities to closely observe and monitor the subjects. Studies conducted in Phase I, usually intended to involve one or a combination of the following objectives: -

(a) Maximum tolerated dose: To determine the tolerability of the dose range expected to be needed for later clinical studies and to determine the nature of adverse reactions that can be expected. These studies include both single and multiple dose administration.

(b) Pharmacokinetics, i.e., characterisation of a drug's absorption, distribution, metabolism and excretion: Although these studies continue throughout the development plan, they should be performed to support formulation development and determine pharmacokinetic parameters in different age groups to support dosing recommendations.

(c) Pharmacodynamics: Depending on the drug and the endpoints studied, pharmacodynamic studies and studies relating to drug blood levels (pharmacokinetic or pharmacodynamic studies) may be conducted in healthy volunteer subjects or in patients with the target disease. If there are appropriate validated indicators of activity and potential efficacy, pharmacodynamic data obtained from patients may guide the dosage and dose regimen to be applied in later studies.

(d) Early measurement of drug activity: Preliminary studies of activity or potential therapeutic benefit may be conducted in Phase I as a secondary objective. Such studies are generally performed in later phases but may be appropriate when drug activity is readily measurable with a short duration of drug exposure in patients at this early stage.

(b) Phase II.— (i) The primary objective of Phase II trials is to evaluate the effectiveness of a drug for a particular indication or indications in patients with the condition under study and to determine the common

short-term side-effects and risks associated with the drug. Studies in Phase II should be conducted in a group of patients who are selected by relatively narrow criteria leading to a relatively homogeneous population. These studies should be closely monitored. An important goal for this phase is to determine the dose and regimen for Phase III trials. Doses used in Phase II are usually (but not always) less than the highest doses used in Phase I.

(ii) Additional objectives of Phase II studies can include evaluation of potential study endpoints, therapeutic regimens (including concomitant medications) and target populations (e.g. mild versus severe disease) for further studies in Phase II or III. These objectives may be served by exploratory analyses, examining subsets of data and by including multiple endpoints in trials.

(c) Phase III.— (i) Phase III studies have primary objective of demonstration or confirmation of therapeutic benefits. Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. These studies should be intended to provide an adequate basis for marketing approval. Studies in Phase III may also further explore the dose-response relationships (relationships among dose, drug concentration in blood and clinical response), use of the drug in wider populations, in different stages of disease, or the safety and efficacy of the drug in combination with other drugs.

(ii) For drugs intended to be administered for long periods, trials involving extended exposure to the drug are ordinarily conducted in Phase III, although they may be initiated in Phase II. These studies carried out in Phase III complete the information needed to support adequate instructions for use of the drug (prescribing information).

(iii) For new drugs approved outside India, Phase III studies may need to be carried out if scientifically and ethically justified, primarily to generate evidence of efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Prior to conduct of Phase III studies in Indian subjects, Central Licencing Authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad.

In case of an application of a new drug already approved and marketed in other country, where local clinical trial in India is waived off or not found scientifically justified for its approval for manufacturing first time in the country, the bioequivalence studies of such drug, as appropriate, is required to be carried out and the test batches manufactured for the purpose shall be inspected before its approval.

(d) Phase IV.— Phase IV or post marketing trial of new drugs are performed after the approval of the drug and related to the approved indication. Such trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition. Such trial might not have been considered essential at the time of new drug approval due to various reasons such as limitation in terms of patient exposure, duration of treatment during clinical development of the drug, need for early introduction of the new drug in the interest of patients etc. Phase IV trials include additional drug-drug interaction, dose response or safety studies and trials design to support use under the approved indication e.g. mortality or morbidity studies, epidemiological studies, etc.

(3) Studies in special populations**.—** Information supporting the use of the drug in children, pregnant women, nursing women, elderly patients, patients with renal or other organ systems failure, and those on specific concomitant medication is required to be submitted if relevant to the clinical profile of the drug and its anticipated usage pattern.

(A) ***Geriatrics*****.—** Geriatric patients should be included in Phase III clinical trials (and in Phase II trials, at the Sponsor's option) in meaningful numbers, if**—**

(a) the disease intended to be treated is characteristically a disease of aging; or

(b) the population to be treated is known to include substantial numbers of geriatric patients; or

(c) when there is specific reason to expect that conditions common in the elderly are likely to be encountered; or

(d) when the new drug is likely to alter the geriatric patient's response (with regard to safety or efficacy) compared with that of the non-geriatric patient.

(B) ***Paediatrics*****.—** (i) The timing of paediatric studies in the new drug development program will depend on the medicinal product, the type of disease being treated, safety considerations, and the efficacy and safety of available treatments. For a drug expected to be used in children, evaluations should be made in the appropriate

age group. When clinical development is to include studies in children, it is usually appropriate to begin with older children before extending the trial to younger children and then infants.

(ii) If the new drug is for diseases predominantly or exclusively affecting paediatric patients, clinical trial data should be generated in the paediatric population except for initial safety and tolerability data, which will usually be obtained in adults unless such initial safety studies in adults would yield little useful information or expose them to inappropriate risk.

(iii) If the new drug is intended to treat serious or life-threatening diseases, occurring in both adults and paediatric patients, for which there are currently no or limited therapeutic options, paediatric population should be included in the clinical trials early, following assessment of initial safety data and reasonable evidence of potential benefit. In circumstances where this is not possible, lack of data should be justified in detail.

(iv) If the new drug has a potential for use in paediatric patients – paediatric studies should be conducted. These studies may be initiated at various phases of clinical development or after post marketing surveillance in adults if a safety concern exists. In cases where there is limited paediatric data at the time of submission of application, more data in paediatric patients would be expected after marketing authorisation for use in children is granted.

(v) The paediatric studies should include—

(a) clinical trials,

(b) relative bioequivalence comparisons of the paediatric formulation with the adult formulation performed in adults, and definitive pharmacokinetic studies for dose selection across the age ranges of paediatric patients in whom the drug is likely to be used. These studies should be conducted in the paediatric patient population with the disease under study.

(vi)If the new drug is a major therapeutic advance for the paediatric population the studies should begin early in the drug development, and this data should be submitted with the new drug application.

(vii) For clinical trials conducted in the paediatric population, the reviewing ethics committee should include members who are knowledgeable about paediatric, ethical, clinical and psychosocial issues.

(C) Pregnant or nursing women.— (i) Pregnant or nursing women should be included in clinical trials only when the drug is intended for use by pregnant or nursing women or fetuses or nursing infants and where the data generated from women who are not pregnant or nursing, is not suitable.

(ii) For new drugs intended for use during pregnancy, follow-up data (pertaining to a period appropriate for that drug) on the pregnancy, foetus and child will be required. Where applicable, excretion of the drug or its metabolites into human milk should be examined and the infant should be monitored for predicted pharmacological effects of the drug.

4. Conduct of Clinical Trial.— Clinical trial should be conducted in accordance with the principles as specified in Third Schedule. Adherence to the clinical trial protocol is essential and if amendment of the protocol becomes necessary the rationale for the amendment shall be provided in the form of a protocol amendment. Serious adverse events shall be reported during clinical trial in accordance with these Rules.

5. Analysis.— The results of a clinical trial shall be analysed according to the plan specified in the clinical trial protocol. Safety data should be appropriately tabulated and all adverse events should be classified according to their seriousness and causal relationship with the study drug.

6. Reporting.— Report of clinical trial shall be documented in accordance with the approaches specified in Table 6 of the Third Schedule. The report shall be certified by the principal investigator or if no principal investigator is designated then by each of the participating investigators of the study.

SECOND SCHEDULE

(*See rules 21, 75, 80 and 97*)

REQUIREMENTS AND GUIDELINES FOR PERMISSION TO IMPORT OR MANUFACTURE OF NEW DRUG FOR SALE OR TO UNDERTAKE CLINICAL TRIAL

1. Application for permission.— (1) Application for permission to import or manufacture new drug for sale or to undertake clinical trials under these Rules shall be made to the Central Licencing Authority accompanied with following data in accordance with the Table 1 or Table 2 or Table 3 or Table 4 of this Schedule, as the case may be, namely:-

(i) chemical and pharmaceutical information;

(ii) animal pharmacology data;

(a) specific pharmacological actions and demonstrating, therapeutic potential for humans shall be described according to the animal models and species used. Wherever possible, dose-response relationships and ED_{50} shall be submitted. Special studies conducted to elucidate mode of action shall also be described;

(b) general pharmacological actions;

(c) pharmacokinetic data related to the absorption, distribution, metabolism and excretion of the test substance. Wherever possible, the drug effects shall be co-related to the plasma drug concentrations;

(iii) animal toxicology data;

(iv) human clinical pharmacology data as prescribed and as stated below:-

(a) for new drug substances discovered or developed in India, clinical trials are required to be carried out in India right from Phase I and data should be submitted as prescribed;

(b) for new drug substances discovered or developed in countries other than India, Phase I data should be submitted along with the application. After submission of Phase I data generated outside India to the Central Licensing Authority, permission may be granted to repeat Phase I trials or to conduct Phase II trials and subsequently Phase III trial concurrently with other global trials for that drug. For a drug going to be introduced for the first time in the country, Phase III trial may be required to be conducted in India before permission to market the drug is granted unless otherwise exempted;

(c) the data required will depend upon the purpose of the new drug application. The number of study subjects and sites to be involved in the conduct of clinical trial will depend upon the nature and objective of the study. Permission to carry out these trials shall generally be given in stages, considering the data emerging from earlier phases;

(d) application for permission to initiate specific phase of clinical trial should also accompany investigator's brochure as per Table 7 of Third Schedule, proposed protocol as per Table 2 of Third Schedule, case record form, trial subject's informed consent document as per Table 3 of Third Schedule, investigator's undertaking as per Table 4 of Third Schedule and ethics committee clearance, if available as per Table 1 of Third Schedule;

(e) reports of clinical studies submitted should be in consonance with the format specified in Table 6 of Third Schedule. The study report shall be certified by the principal investigator or, if no principal investigator is designated, then by each of the investigators participating in the study. The certification should acknowledge the contents of the report, the accurate presentation of the study was undertaken, and express agreement with the conclusions. Each page should be numbered;

(v) regulatory status in other countries as prescribed including information in respect of restrictions imposed, if any, on the use of the drug in other countries, e.g. dosage limits, exclusion of certain age groups, warning about adverse drug reactions etc. Likewise, if the drug has been withdrawn in any country by the manufacturer or by regulatory authorities, such information should also be furnished along with the reasons and their relevance, if any, to India. This information must continue to be submitted by the sponsor to the Central Licencing Authority during the course of marketing of the drug in India;

(vi) the full prescribing information should be submitted as part of the new drug application for marketing. The format of prescribing information is specified in Table 8 of Third Schedule.

(vii) all package inserts, promotional literature and patient education material subsequently produced are required to be consistent with the contents of the approved full prescribing information. The drafts of label and carton texts should comply with provisions of rule 96 and rule 97 of the Drugs and Cosmetics Rules, 1945. After submission and approval by the Central Licencing Authority, no changes in the package insert shall be effected without such changes being approved by the Central Licencing Authority;

(viii) complete testing protocol for quality control testing together with a complete impurity profile and release specifications for the product as prescribed should be submitted as part of new drug application for marketing. Samples of the pure drug substance and finished product are to be submitted when desired by the regulatory authority;

(ix) if the application is for the conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and patients as well as the justification for undertaking such trials in India should be provided to the Central Licencing Authority along with the application.

(2) Special situations for a new drug where relaxation, abbreviations, omission or deferment of data may be considered. - (i) Depending on categories and nature of new drugs to be imported or manufactured for sale or clinical trial to be undertaken (viz. New Chemical Entity, biological products, similar biologics, approved new drug or new dosage form or new indication or new route of administration or new strength of already approved drugs, etc.,) requirements of chemical and pharmaceutical information, animal pharmacology and toxicology data, clinical data may differ. The requirements may also differ depending on the specific phase of clinical trial proposed to be conducted as well as clinical parameters related to the specific study drug.

(ii) For drugs intended to be used in life threatening or serious disease conditions or rare diseases and for drugs intended to be used in the diseases of special relevance to Indian scenario or unmet medical need in India, disaster or special defence use e.g. haemostatic and quick wound healing, enhancing oxygen carrying capacity, radiation safety, drugs for combating chemical, nuclear, biological infliction etc., following mechanism may be followed to expedite the development of new drug and approval process.

(A) Accelerated Approval Process: Accelerated approval process may be allowed to a new drug for a disease or condition, taking into account its severity, rarity, or prevalence and the availability or lack of alternative treatments, provided that there is a prima facie case of the product being of meaningful therapeutic benefit over the existing treatment.

(a) In such case, the approval of the new drug may be based on data generated in clinical trial where surrogate endpoint shall be considered rather than using standard outcome measures such as survival or disease progression, which are reasonably likely to predict clinical benefit, or a clinical endpoint. These should be measurable earlier than irreversible morbidity or mortality (IMM) and reasonably likely to predict clinical benefit.

(b) After granting accelerated approval for such drug, the post marketing trials shall be required to validate the anticipated clinical benefit.

(c) Accelerated approval may also be granted to a new drug if it is intended for the treatment of a serious or life-threatening condition or disease of special relevance to the country, and addresses unmet medical needs. This provision is intended to facilitate and expedite review of drugs so that an approved product can reach the therapeutic armamentarium expeditiously.

(d) If the remarkable efficacy is observed with a defined dose in the Phase II clinical trial of investigational new drug for the unmet medical needs of serious and life threatening diseases in the country, it may be considered for grant of marketing approval by the Central Licencing Authority based on Phase II clinical trial data. In such cases, additional post licensure studies may be required to be conducted after approval to generate the data on larger population to further verify and describe the clinical benefits, as per the protocol approved by the Central Licencing Authority.

(e) The type of information needed to demonstrate the potential of a drug to address an unmet medical need will depend on the stage of drug development. Early in development, such potential should be sufficiently demonstrated based on nonclinical models, a mechanistic rationale and pharmacologic data. Later in development, prior to new drug approval such potential should be demonstrated through clinical data to address an unmet medical need.

Explanation. - For the purpose of this clause, an unmet medical need is a situation where treatment or diagnosis of disease or condition is not addressed adequately by available therapy. An unmet medical need includes an immediate need for a defined population (i.e., to treat a serious condition with no or limited treatment) or a longer-term need for society (e.g., to address the development of resistance to antibacterial drugs).

(B) Situations where quick or expeditious review process can be sought for approval of a new drug after clinical development: - (i) In situation where the evidence for clinical safety and efficacy have been established even if the drug has not completed the all or normal clinical trial phases, the sponsor or applicant may apply to the licencing authority for expedited review process wherein the licencing authority will examine and satisfy the following conditions. -

(a) it is for a drug that is intended to treat a serious or life threatening or rare disease or condition;

(b) if approved, the drug would provide a significant advantage in terms of safety or efficacy;

(c) there is substantial reduction of a treatment-limiting adverse reaction and enhancement of patient compliance that is expected to lead to an improvement in serious outcomes;

(ii) the sponsor or applicant may also apply to the licencing authority for expedited review process for new drugs developed for disaster or defence use in extraordinary situation, such as war time, the radiation exposure by accident or intention, sudden deployment of forces at areas with higher health risk, where specific preventive and treatment strategy is required, where new intervention in the form of new drug, route of delivery or formulation has been developed and where real life clinical trial may not be possible. The permission for manufacture of such new drug may be granted if following conditions are satisfied: -

(a) The preclinical data makes a case for claimed efficacy;

(b) there is no possibility of obtaining informed consent from the patient or his legally acceptable representative, as the case may be, adopting inclusion and exclusion criteria and strict protocol adherence by each subject;

(c) there is no established management or therapeutic strategy available as on date and proposed intervention has clear possible advantage;

(d) such approval can be used only for one time. The subsequent approval shall only be granted once detailed efficacy report of such intervention is generated.

(iii) the new drug is an orphan drug as defined in clause (x) of rule 2 of these Rules.

(3) Requirements of data and information for permission to import or manufacture of a drug already approved which is now proposed to be clinically tried or marketed with certain new claims. – (i) In case a drug already approved by the Central Licencing Authority for certain claims, which is now proposed to be clinically tried or marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration or novel drug delivery system (NDDS), the requirements of data and information for permission to import or manufacture of such new drug for sale or to undertake clinical trial shall depend on nature and regulatory status of the drug for the new claim in other country. Application for approval of manufacture or import of such new drug or to undertake Clinical trial may differ from application for a new drug molecule in that they allow the applicant and regulatory authority to rely at least in part, on the safety or efficacy data of drug formulation already approved. However, additional non-clinical or clinical data may be necessary to substantiate the new claims considering the following:-

(A) Chemical and pharmaceutical information will be same as prescribed in this Schedule. However, the data requirements may be omitted depending on whether the drug formulation is already approved and marketed in the country by the applicant in the same dosage form for certain indication. If it is approved and marketed, no further chemical and pharmaceutical data is required to be submitted.

(B) The animal pharmacological and toxicological data and clinical data needed in such cases will usually be determined on case-by-case basis depending on the type of new claims being made by the applicant as well as the mechanism of action, patho-physiology of the disease or condition, safety and efficacy profile in the respective conditions or population and clinical data already generated with the drug in the approved claim. The

requirements may be abbreviated or relaxed or omitted as considered appropriate by the Central Licencing Authority under following conditions:

(a) the drug is already approved and marketed in other country for the proposed new claim;

(b) clinical data supporting the benefit-risk ratio in favour of the drug in the proposed new claim is available;

(c) the clinical trial doesn't involve a route of administration, dose, patient population that significantly increases the risk associated with the use of the drug.

(ii) In case of an application for permission to undertake clinical trial of a new drug formulation, which is already approved in the country, no chemical and pharmaceutical data and non-clinical and clinical data is required to be submitted provided the clinical trial is proposed to be conducted with a new drug manufactured or imported by a firm under necessary new drug permission or import registration and licence, as the case may be granted by the Central Licencing Authority.

Note: The data requirements stated in this Schedule are expected to provide adequate information to evaluate the efficacy, safety and therapeutic rationale of new drugs prior to the permission for sale. Depending upon the nature of new drugs and diseases, additional information may be required by the Central Licencing Authority. The applicant shall certify the authenticity of the data and documents submitted in support of an application for new drug. The Central Licencing Authority reserves the right to reject any data or any documents if such data or contents of such documents are found to be of doubtful integrity.

2. Animal toxicology (Non-clinical toxicity studies).- (1) General principles. - Toxicity studies should comply with the norms of Good Laboratory Practices (GLP). Briefly, these studies should be performed by suitably trained and qualified staff employing properly calibrated and standardized equipment of adequate size and capacity. Studies should be done as per written protocols with modifications (if any) verifiable retrospectively. Standard operating procedures (SOPs) should be followed for all managerial and laboratory tasks related to these studies. Test substances and test systems (in-vitro or in-vivo) should be properly characterised and standardized. All documents belonging to each study, including its approved protocol, raw data, draft report, final report, and histology slides and paraffin tissue blocks should be preserved for a minimum of five years after marketing of the drug.

Toxicokinetic studies (generation of pharmacokinetic data either as an integral component of the conduct of non-clinical toxicity studies or in specially designed studies) should be conducted to assess the systemic exposure achieved in animals and its relationship to dose level and the time course of the toxicity study. Other objectives of toxicokinetic studies include obtaining data to relate the exposure achieved in toxicity studies to toxicological findings and contribute to the assessment of the relevance of these findings to clinical safety, to support the choice of species and treatment regimen in nonclinical toxicity studies and to provide information which, in conjunction with the toxicity findings, contributes to the design of subsequent non-clinical toxicity studies.

(1.1) Systemic toxicity studies,-

(1.1.1) Single-dose toxicity studies.— These studies (see Table 1) should be carried out in 2 rodent species (mice and rats) using the same route as intended for humans. In addition, unless the intended route of administration in humans is only intravenous, at least one more route should be used in one of the species to ensure systemic absorption of the drug. This route should depend on the nature of the drug. A limit of 2g/kg (or 10 times the normal dose that is intended in humans, whichever is higher) is recommended for oral dosing. Animals should be observed for 14 days after the drug administration, and Minimum Lethal Dose (MLD) and Maximum Tolerated Dose (MTD) should be established. If possible, the target organ of toxicity should also be determined. Mortality should be observed for up to seven days after parenteral administration and up to 14 days after oral administration. Symptoms, signs and mode of death should be reported, with appropriate macroscopic and microscopic findings where necessary. LD_{10} and LD_{50} should be reported preferably with 95 percent confidence limits. If LD_{50} cannot be determined, reasons for the same should be stated.

The dose causing severe toxic manifestations or death should be defined in the case of cytotoxic anticancer agents, and the post-dosing observation period should be up to 14 days. Mice should first be used for determination of MTD. Findings should then be confirmed in rat for establishing linear relationship between toxicity and body surface area. In case of nonlinearity, data of the more sensitive species should be used to determine the Phase I starting dose. Where rodents are known to be poor

predictors of human toxicity (e.g., antifolates), or where the cytotoxic drug acts by a novel mechanism of action, Maximum Tolerated Dose (MTD) should be established in non-rodent species.

(1.1.2) Repeated-dose systemic toxicity studies.— These studies (see Table 1) should be carried out in at least two mammalian species, of which one should be a non-rodent. Dose ranging studies should precede the 14-, 28-, 90- or 180- day toxicity studies. Duration of the final systematic toxicity study will depend on the duration, therapeutic indication and scale of the proposed clinical trial. If a species is known to metabolise the drug in the same way as humans, it should be preferred for toxicity studies.

In repeated-dose toxicity studies the drug should be administered seven days a week by the route intended for clinical use. The number of animals required for these studies, i.e. the minimum number of animals on which data should be available.

Wherever applicable, a control group of animals given the vehicle alone should be included, and three other groups should be given graded doses of the drug. The highest dose should produce observable toxicity; the lowest dose should not cause observable toxicity, but should be comparable to the intended therapeutic dose in humans or a multiple of it. To make allowance for the sensitivity of the species the intermediate dose should cause some symptoms, but not gross toxicity or death, and should be placed logarithmically between the other two doses.

The parameters to be monitored and recorded in long-term toxicity studies should include behavioural, physiological, biochemical and microscopic observations. In case of parenteral drug administration, the sites of injection should be subjected to gross and microscopic examination. Initial and final electrocardiogram and fundus examination should be carried out in the non-rodent species.

In the case of cytotoxic anticancer agents dosing and study design should be in accordance with the proposed clinical schedule in terms of days of exposure and number of cycles. Two rodent species may be tested for initiating Phase I trials. A non-rodent species should be added if the drug has a novel mechanism of action, or if permission for Phase II, III or marketing is being sought.

For most compounds, it is expected that single dose tissue distribution studies with sufficient sensitivity and specificity will provide an adequate assessment of tissue distribution and the potential for accumulation. Thus, repeated dose tissue distribution studies should not be required uniformly for all compounds and should only be conducted when appropriate data cannot be derived from other sources. Repeated dose studies may be appropriate under certain circumstances based on the data from single dose tissue distribution studies, toxicity and toxicokinetic studies. The studies may be most appropriate for compounds which have an apparently long half-life, incomplete elimination or unanticipated organ toxicity.

Notes: (i) Single dose toxicity study. - Each group should contain at least five animals of either sex. At least four graded doses should be given. Animals should be exposed to the test substance in a single bolus or by continuous infusion or several doses within 24 hours. Animals should be observed for 14 days. Signs of intoxication, effect on body weight, gross pathological changes should be reported. It is desirable to include histo-pathology of grossly affected organs, if any.

(ii) Dose-ranging study. - Objectives of this study include the identification of target organ of toxicity and establishment of Maximum Tolerated Dose (MTD) for subsequent studies.

(a) Rodents. - Study should be performed in one rodent species (preferably rat) by the proposed clinical route of administration. At least four graded doses including control should be given, and each dose group as well as the vehicle control should consist of a minimum of five animals of each sex. Animals should be exposed to the test substance daily for 10 consecutive days. Highest dose should be the maximum tolerated dose of single-dose study. Animals should be observed daily for signs of intoxication (general appearance, activity and behavior etc), and periodically for the body weight and laboratory parameters. Gross examination of viscera and microscopic examination of affected organs should be done.

(b) Non-rodents. - One male and one female are to be taken for ascending Phase Maximum Tolerated Dose (MTD) study. Dosing should start after initial recording of cage-side and laboratory parameters. Starting dose may be three to five times the extrapolated effective dose or Maximum Tolerated Dose (MTD) (whichever is less), and dose escalation in suitable steps should be done every third day after drawing the samples for laboratory parameters. Dose should

be lowered appropriately when clinical or laboratory evidence of toxicity are observed. Administration of test substance should then continue for 10 days at the well-tolerated dose level following which, samples for laboratory parameters should be taken. Sacrifice, autopsy and microscopic examination of affected tissues should be performed as in the case of rodents.

(iii) 14-28 Day repeated-dose toxicity studies. - One rodent (6-10/sex/group) and one non-rodent (2-3/sex/group) species are needed. Daily dosing by proposed clinical route at three dose levels should be done with highest dose having observable toxicity, mid dose between high and low dose, and low dose. The doses should preferably be multiples of the effective dose and free from toxicity. Observation parameters should include cage side observations, body weight changes, food or water intake, blood biochemistry, haematology, and gross and microscopic studies of all viscera and tissues.

(iv) 90 Days repeated-dose toxicity studies. - One rodent (15-30/sex/group) and one non-rodent (4-6/sex/group) species are needed. Daily dosing by proposed clinical route at three graded dose levels should be done. In addition to the control a "high-dose-reversal" group and its control group should be also included. Parameters should include signs of intoxication (general appearance, activity and behavior etc), body weight, food intake, blood biochemical parameters, haematological values, urine analysis, organ weights, gross and microscopic study of viscera and tissues. Half the animals in "reversal" groups (treated and control) should be sacrificed after 14 days of stopping the treatment. The remaining animals should be sacrificed after 28 days of stopping the treatment or after the recovery of signs or clinical pathological changes – whichever comes later, and evaluated for the parameters used for the main study.

(v) 180-Day repeated-dose toxicity studies. - One rodent (15-30/sex/group) and one non-rodent (4-6/sex/group) species are needed. At least four groups, including control, should be taken. Daily dosing by proposed clinical route at three graded dose levels should be done. Parameters should include signs of intoxication, body weight, food intake, blood biochemistry, hematology, urine analysis, organ weights, gross and microscopic examination of organs and tissues.

(1.2) Male fertility study: One rodent species (preferably rat) should be used. Dose selection should be done from the results of the previous 14 days or 28 days toxicity study in rat. Three dose groups, the highest one showing minimal toxicity in systemic studies, and a control group should be taken. Each group should consist of six adult male animals. Animals should be treated with the test substance by the intended route of clinical use for minimum 28 days and maximum 70 days before they are paired with female animals of proven fertility in a ratio of 1:2 for mating. Drug treatment of the male animals should continue during pairing. Pairing should be continued till the detection of vaginal plug or 10 days, whichever is earlier. Females getting thus pregnant should be examined for their fertility index after day 13 of gestation. All the male animals should be sacrificed at the end of the study. Weights of each testis and epididymis should be separately recorded. Sperms from one epididymis should be examined for their motility and morphology. The other epididymis and both testes should be examined for their histology.

(1.3) Female reproduction and developmental toxicity studies: These studies need to be carried out for all drugs proposed to be studied or used in women of child bearing age. Segment I, II and III studies (see below) are to be performed in albino mice or rats, and segment II study should include albino rabbits also as a second test species. On the occasion, when the test article is not compatible with the rabbit (e.g. antibiotics which are effective against gram positive, anaerobic organisms and protozoas) the Segment II data in the mouse may be substituted.

(1.3.1) Female fertility study (Segment I). - The study should be done in one rodent species (rat preferred). The drug should be administered to both males and females, beginning a sufficient number of days (28 days in males and 14 days in females) before mating. Drug treatment should continue during mating and, subsequently, during the gestation period. Three graded doses should be used, the highest dose (usually the Maximum Tolerated Dose (MTD) obtained from previous systemic toxicity studies) should not affect general health of the parent animals. At least 15 males and 15 females should be used per dose group. Control and the treated groups should be of similar size. The route of administration should be the same as intended for therapeutic use.

Dams should be allowed to litter and their medication should be continued till the weaning of pups. Observations on body weight, food intake, clinical signs of intoxication, mating behaviour, progress of

gestation or parturition periods, length of gestation, parturition, postpartum health and gross pathology (and histopathology of affected organs) of dams should be recorded. The pups from both treated and control groups should be observed for general signs of intoxication, sex-wise distribution in different treatment groups, body weight, growth parameters, survival, gross examination, and autopsy. Histopathology of affected organs should be done.

(1.3.2) Teratogenicity study (Segment II). - One rodent (preferably rat) and one non-rodent (rabbit) species are to be used. The drug should be administered throughout the period of organogenesis, using three dose levels as described for segment I. The highest dose should cause minimum maternal toxicity and the lowest one should be proportional to the proposed dose for clinical use in humans or a multiple of it. The route of administration should be the same as intended for human therapeutic use.

The control and the treated groups should consist of at least 20 pregnant rats (or mice) and 12 rabbits, on each dose level. All foetuses should be subjected to gross examination, one of the foetuses should be examined for skeletal abnormalities and the other half for visceral abnormalities. Observation parameters should include: (Dams) signs of intoxication, effect on body weight, effect on food intake, examination of uterus, ovaries and uterine contents, number of corpora lutea, implantation sites, resorptions (if any); and for the foetuses, the total number, gender, body length, weight and gross or visceral or skeletal abnormalities, if any.

(1.3.3) Perinatal study (Segment III). - This study is specially recommended if the drug is to be given to pregnant or nursing mothers for long periods or where there are indications of possible adverse effects on foetal development. One rodent species (preferably rat) is needed. Dosing at levels comparable to multiples of human dose should be done by the intended clinical route. At least four groups (including control), each consisting of 15 dams should be used. The drug should be administered throughout the last trimester of pregnancy (from day 15 of gestation) and then the dose that causes low foetal loss should be continued throughout lactation and weaning. Dams should then be sacrificed and examined as described below.

One male and one female from each litter of F1 generation (total 15 males and 15 females in each group) should be selected at weaning and treated with vehicle or test substance (at the dose levels described above) throughout their periods of growth to sexual maturity, pairing, gestation, parturition and lactation. Mating performance and fertility of F1 generation should thus be evaluated to obtain the F2 generation whose growth parameters should be monitored till weaning. The criteria of evaluation should be the same as described earlier.

Animals should be sacrificed at the end of the study and the observation parameters should include (Dams) body weight, food intake, general signs of intoxication, progress of gestation or parturition periods and gross pathology (if any); and for pups, the clinical signs, sex-wise distribution in dose groups, body weight, growth parameters, gross examination, survival and autopsy (if needed) and where necessary, histopathology.

(1.4) Local toxicity.- These studies are required when the new drug is proposed to be used by some special route (other than oral) in humans. The drug should be applied to an appropriate site (e.g., skin or vaginal mucous membrane) to determine local effects in a suitable species. Typical study designs for these studies should include three dose levels and untreated or vehicle control, preferably use of two species, and increasing group size with increase in duration of treatment. Where dosing is restricted due to anatomical or humane reasons, or the drug concentration cannot be increased beyond a certain level due to the problems of solubility, pH or tonicity, a clear statement to this effect should be given. If the drug is absorbed from the site of application, appropriate systemic toxicity studies will also be required.

Notes: (i) *Dermal toxicity study*. - The study may be done in rabbit and rat. The initial toxicity study shall be carried out by non-animal alternative tests as given in Organisation for Economic Cooperation and Development Guidelines. In rabbit and rat studies, daily topical (dermal) application of test substance in its clinical dosage form should be done.; Test material should be applied on shaved skin covering not less than 10% of the total body surface area. Porous gauze dressing should be used to hold liquid material in place. Formulations with different concentrations (at least 3) of test substance, several fold higher than the clinical dosage form should be used. Period of application may vary from seven to 90 days depending on the clinical duration of use. Where skin irritation is grossly visible in the initial studies, a recovery group should be included in the subsequent

repeated-dose study. Local signs (erythema, oedema and eschar formation) as well as histological examination of sites of application should be used for evaluation of results.

(ii) ***Photo-allergy or dermal photo-toxicity***. - It should be tested by Armstrong or Harber test in guinea pig. This test should be done if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential (e.g., drugs to be used in treatment of leucoderma). Pretest in eight animals should screen four concentrations (patch application for two hours ±15 min.) with and without UV exposure (10 J/cm2). Observations recorded at 24 and 48 hours should be used to ascertain highest non-irritant dose. Main test should be performed with 10 test animals and five controls. Induction with the dose selected from pretest should use 0.3 ml/patch for 2 hour ±15 min. followed by 10 J/cm2 of UV exposure. This should be repeated on day 0, 2,4,7,9 and 11 of the test. Animals should be challenged with the same concentration of test substance between day 20 to 24 of the test with a similar 2-hour application followed by exposure to 10 J/cm2 of UV light. Examination and grading of erythema and oedema formation at the challenge sites should be done 24 and 48 hours after the challenge. A positive control like musk ambrett or psoralin should be used.

(iii) ***Vaginal toxicity test*. -** Study is to be done in rabbit or dog. Test substance should be applied topically (vaginal mucosa) in the form of pessary, cream or ointment. Six to ten animals per dose group should be taken. Higher concentrations or several daily applications of test substance should be done to achieve multiples of daily human dose. The minimum duration of drug treatment is seven days (more according to clinical use), subject to a maximum of 30 days. Observation parameters should include swelling, closure of in troit us and histopathology of vaginal wall.

(iv) ***Rectal tolerance test*.**- For all preparations meant for rectal administration this test may be performed in rabbits or dogs. Six to ten animals per dose group should be taken. Formulation in volume comparable to human dose (or the maximum possible volume) should be applied once or several times daily, per rectally, to achieve administration of multiples of daily human dose. The minimum duration of application is seven days (more according to clinical use), subject to a maximum of 30 days. Size of suppositories may be smaller, but the drug content should be several fold higher than the proposed human dose. Observation parameters should include clinical signs (sliding on backside), signs of pain, blood or mucus in faeces, condition of anal region or sphincter, gross and (if required) histological examination of rectal mucosa.

(v) ***Parenteral drugs*.-** For products meant for intravenous or intramuscular or subcutaneous or intradermal injection the sites of injection in systemic toxicity studies should be specially examined grossly and microscopically. If needed, reversibility of adverse effects may be determined on a case to case basis.

(vi) ***Ocular toxicity studies (for products meant for ocular instillation). -*** These studies should be carried out in two species, one of which should be the albino rabbit which has a sufficiently large conjunctival sac. Direct delivery of drug onto the cornea in case of animals having small conjunctival sacs should be ensured. Liquids, ointments, gels or soft contact lenses (saturated with drug) should be used. Initial single dose application should be done to decide the exposure concentrations for repeated-dose studies and the need to include a recovery group. Such initial toxicity studies shall be carried out by non-animal alternative tests as given in Organisation for Economic Cooperation and Development Guidelines. Duration of the final study will depend on the proposed length of human exposure subject to a maximum of 90 days. At least two different concentrations exceeding the human dose should be used for demonstrating the margin of safety. In acute studies, one eye should be used for drug administration and the other kept as control. A separate control group should be included in repeated-dose studies. Slit-lamp examination should be done to detect the changes in cornea, iris and aqueous humor. Fluorescent dyes (sodium fluorescein, 0.25 to 1.0%) should be used for detecting the defects in surface epithelium of cornea and conjunctiva. Changes in intra-ocular tension should be monitored by a tonometer. Histological examination of eyes should be done at the end of the study after fixation in Davidson's or Zenker's fluid.

(vii) ***Inhalation toxicity studies*. -** The studies are to be undertaken in one rodent and one non-rodent species using the formulation that is to be eventually proposed to be marketed. Acute, subacute and chronic toxicity studies should be performed according to the intended duration of human exposure. Standard systemic toxicity study designs (described above) should be used. Gases and vapours should be given in whole body exposure chambers; aerosols are to be given by nose-only method. Exposure time and concentrations of test substance (limit dose of 5mg/l) should be adjusted to ensure exposure at levels comparable to multiples of intended human exposure. Three dose groups and a control (plus vehicle control, if needed) are required.

Duration of exposure may vary subject to a maximum of 6 hours per day and five days a week. Food and water should be withdrawn during the period of exposure to test substance.

Temperature, humidity and flow rate of exposure chamber should be recorded and reported. Evidence of exposure with test substance of particle size of 4 micron (especially for aerosols) with not less than 25% being 1 micron should be provided. Effects on respiratory rate, findings of bronchial lavage fluid examination, histological examination of respiratory passages and lung tissue should be included along with the regular parameters of systemic toxicity studies or assessment of margin of safety.

(1.5) Allergenicity or Hypersensitivity. - Standard tests include guinea pig maximization test (GPMT) and local lymph node assay (LLNA) in mouse. Any one of the two may be done.

Notes: (i) Guinea pig maximization test. - The test is to be performed in two steps; first, determination of maximum non-irritant and minimum irritant doses, and second, the main test. The initial study will also have two components. To determine the intradermal induction dose, four dose levels should be tested by the same route in a batch of four male and four female animals (2 of each sex should be given Freund's adjuvant). The minimum irritant dose should be used for induction. Similarly, a topical minimum irritant dose should be determined for challenge. This should be established in two males and two females. A minimum of six male and six female animals per group should be used in the main study. One test and one control group should be used. It is preferable to have one more positive control group. Intradermal induction (day 1) coupled with topical challenge (day21) should be done. If there is no response, re-challenge should be done 7 to 30days after the primary challenge. Erythema and oedema (individual animal scores as well as maximization grading) should be used as evaluation criteria.

(ii) Local lymph node assay. - Mice used in this test should be of the same sex, either only males or only females. Drug treatment is to be given on ear skin. Three graded doses, the highest being maximum non-irritant dose plus vehicle control should be used. A minimum of 6 mice per group should be used. Test material should be applied on ear skin on three consecutive days and on day 5, the draining auricular lymph nodes should be dissected out 5 hours after i.v. H-thymidine or bromo-deoxy-uridine (BrdU). Increase in H-thymidine or BrdU incorporation should be used as the criterion for evaluation of results.

(1.6) Genotoxicity.— Genotoxic compounds, in the absence of other data, shall be presumed to be trans-species carcinogens, implying a hazard to humans. Such compounds need not be subjected to long term carcinogenicity studies. However, if such a drug is intended to be administered for chronic illnesses or otherwise over a long period of time - a chronic toxicity study (up to one year) may be necessary to detect early tumorigenic effects. Genotoxicity tests are in vitro and in vivo tests conducted to detect compounds which induce genetic damage directly or indirectly. These tests should enable a hazard identification with respect to damage to De-oxy Ribonucleic Acid (DNA) and its fixation.

The following standard test battery is generally expected to be conducted:

(i) A test for gene mutation in bacteria.

(ii) An in vitro test with cytogenetic evaluation of chromosomal damage with mammalian cells or an in vitro mouse lymphomatic assay.

(iii) An in vivo test for chromosomal damage using rodent haematopoietic cells. Other genotoxicity tests e.g. tests for measurement of De-oxy Ribonucleic Acid (DNA) adducts, De-oxy Ribonucleic Acid (DNA) strand breaks, De-oxy Ribonucleic Acid (DNA) repair or recombination serve as options in addition to the standard battery for further investigation of genotoxicity test results obtained in the standard battery. Only under extreme conditions in which one or more tests comprising the standard battery cannot be employed for technical reasons, alternative validated tests can serve as substitutes provided sufficient scientific justification should be provided to support the argument that a given standard battery test is not appropriate.

(iv) Both in-vitro and in-vivo studies should be done. In-vitro studies should include Ames Salmonella assay and chromosomal aberrations (CA) in cultured cells. In-vivo studies should include micronucleus assay (MNA) or chromosomal aberrations (CA) in rodent bone marrow. Data analysis of chromosomal aberrations (CA) should include analysis of “gaps”.

(v) Cytotoxic anticancer agents. - Genotoxicity data are not required before Phase I and II trials. But these studies should be completed before applying for Phase III trials.

Notes: *Ames' Test (Reverse mutation assay in Salmonella):* S. typhimurium tester strains such as TA98, TA100, TA102, TA1535, TA97 or Escherichia coli WP2 uvrA or Escherichia coli WP2 uvrA (pKM101) should be used.

(vi) In-vitro exposure (with and without metabolic activation, S9 mix) should be done at a minimum of 5 log dose levels. "Solvent" and "positive" control should be used. Positive control may include 9-amino-acridine, 2-nitrofluorine, sodium azide and mitomycin C, respectively, in the tester strains mentioned above. Each set should consist of at least three replicates. A 2.5 fold (or more) increase in number of revertants in comparison to spontaneous revertants would be considered positive.

(vii) In-vitro cytogenetic assay. - The desired level of toxicity for in vitro cytogenetic tests using cell lines should be greater than 50% reduction in cell number or culture confluency. For lymphocyte cultures, an inhibition of mitotic index by greater than 50% is considered sufficient. It should be performed in Chinese Hamster Ovary (CHO) cells or on human lymphocyte in culture. In-vitro exposure (with and without metabolic activation, S9 mix) should be done using a minimum of 3 log doses. "Solvent" and "positive" control should be included. A positive control like Cyclophosphamide with metabolic activation and Mitomycin C for without metabolic activation should be used to give a reproducible and detectable increase clastogenic effect over the background which demonstrates the sensitivity of the test system. Each set should consist of at least three replicates. Increased number of aberrations in metaphase chromosomes should be used as the criteria for evaluation.

(viii) In-vivo micronucleus assay. - One rodent species (preferably mouse) is needed. Route of administration of test substance should be the same as intended for humans. Five animals per sex per dose groups should be used. At least three dose levels, plus "solvent" and "positive" control should be tested. A positive control like mitomycin C or cyclophosphamide should be used. Dosing should be done on day one and two of study followed by sacrifice of animals six hours after the last injection. Bone marrow from both the femora should be taken out, flushed with fetal bovine serum (20 min.), pelletted and smeared on glass slides. Giemsa-May Gruenwald staining should be done and increased number of micronuclei in polychromatic erythrocytes (minimum 1000) should be used as the evaluation criteria.

(ix) In-vivo cytogenetic assay. - One rodent species (preferably rat) is to be used. Route of administration of test substance should be the same as intended for humans. Five animals/sex/dose groups should be used. At least three dose levels, plus "solvent" and "positive" control should be tested. Positive control may include cyclophosphamide. Dosing should be done on day one followed by intra-peritoneal colchicine administration at 22 hours. Animals should be sacrificed two hours after colchicine administration. Bone marrow from both the femora should be taken out, flushed with hypotonic saline (20 minutes), pelletted and resuspended in Carnoy's fluid. Once again the cells should be pelletted and dropped on clean glass slides with a Pasteur pipette. Giemsa staining should be done and increased number of aberrations in metaphase chromosomes (minimum 100) should be used as the evaluation criteria.

(1.7) Carcinogenicity.- Carcinogenicity studies should be performed for all drugs that are expected to be clinically used for more than six months as well as for drugs used frequently in an intermittent manner in the treatment of chronic or recurrent conditions. Carcinogenicity studies are also to be performed for drugs if there is concern about their carcinogenic potential emanating from previous demonstration of carcinogenic potential in the product class that is considered relevant to humans or where structure-activity relationship suggests carcinogenic risk or when there is evidence of preneoplastic lesions in repeated dose toxicity studies or when long-term tissue retention of parent compound or metabolites results in local tissue reactions or other pathophysiological responses. For pharmaceuticals developed to treat certain serious diseases, Central Licencing Authority may allow carcinogenicity testing to be conducted after marketing permission has been granted.

In instances where the life-expectancy in the indicated population is short (i.e., less than 2 - 3 years) no long-term carcinogenicity studies may be required. In cases where the therapeutic agent for cancer is generally successful and life is significantly prolonged there may be later concerns regarding secondary cancers. When such drugs are intended for adjuvant therapy in tumour free patients or for prolonged use in non-cancer indications, carcinogenicity studies may be needed. Completed rodent carcinogenicity studies are not needed in advance of the conduct of large scale clinical trials, unless there is special concern for the patient population.

Carcinogenicity studies should be done in a rodent species (preferably rat). Mouse may be employed only with proper scientific justification. The selected strain of animals should not have a very high or very low incidence of spontaneous tumors.

At least three dose levels should be used. The highest dose should be sub-lethal, and it should not reduce the life span of animals by more than 10% of expected normal. The lowest dose should be comparable to the intended human therapeutic dose or a multiple of it, e.g. 2.5x; to make allowance for the sensitivity of the species. The intermediate dose to be placed logarithmically between the other two doses. An untreated control and (if indicated) a vehicle control group should be included. The drug should be administered seven days a week for a fraction of the life span comparable to the fraction of human life span over which the drug is likely to be used therapeutically. Generally, the period of dosing should be 24 months for rats and 18 months for mice.

Observations should include macroscopic changes observed at autopsy and detailed histopathology of organs and tissues. Additional tests for carcinogenicity (short-term bioassays, neonatal mouse assay or tests employing transgenic animals) may also be done depending on their applicability on a case to case basis.

Note: Each dose group and concurrent control group not intended to be sacrificed early should contain at least 50 animals of each sex. A high dose satellite group for evaluation of pathology other than neoplasia should contain 20 animals of each sex while the satellite control group should contain10animals of each sex. Observation parameters should include signs of intoxication, effect on body weight, food intake, clinical chemistry parameters, hematology parameters, urine analysis, organ weights, gross pathology and detailed histopathology. Comprehensive descriptions of benign and malignant tumour development, time of their detection, site, dimensions, histological typing etc. should be given.

(1.8) Animal toxicity requirements for clinical trials and marketing of a new drug.

Systemic Toxicity Studies			
Route of administration	Duration of proposed human administration	Human Phase(s) for which study is proposed to be conducted	Long term toxicity requirements
Oral or Parenteral or Transdermal	Single dose or several doses in one day, up to 1 week	I, II, III	2 species; 2 weeks
	>1 week but upto 2 weeks	I, II, III	2 species; 2weeks
	Upto 2 weeks	Marketing permission	2 species; 4weeks
	>2 weeks but upto 4 weeks	I, II,III	2 species; equal to duration of human exposure
		Marketing permission	2 species; 12 weeks
	> 4 weeks but upto 12 weeks	I,II,III	2 species; equal to duration of human exposure
		Marketing permission	2 species; 24 weeks
	> 12 weeks but upto 24 weeks	I,II,III	2 species; equal to duration of human exposure
		Marketing permission	2 species; Rodent 24 weeks, non-rodent 36 weeks
	> 24 weeks	I,II,III	2 species; Rodent 24 weeks, non-rodent 36weeks

		Marketing permission	2 species; Rodent 24 weeks, non-rodent 36 weeks
Inhalation (general Anaesthetics, aerosols)	Up to 2 weeks	I, II, III	2 species; I month (Exposure time 3h/d, 5d/week)
	Up to 4 weeks	I, II, III	2 species; 12 weeks (Exposure time 6h/d, 5d/week)
	>14 weeks	I, II, III	2 sp; 24 weeks (Exposure time 6h/d, 5d/week)
Local Toxicity Studies			
Dermal	Up to 2 weeks	I, II	1 species; 4 weeks
		III	2 species; 4 weeks
	> 2 weeks	I, II, III	2 species; 12 weeks
Ocular or Optic or Nasal	Up to 2 weeks	I, II	1 species; 4 weeks
		III	2 species; 4 weeks
	> 2 weeks	I, II, III	2 species; 12 weeks
Vaginal or Rectal	Up to 2 weeks	I, II	1 species; 4weeks
		III	2 species; 4 weeks
	> 2 weeks	I, II, III	2 species; 12 weeks

Special Toxicity Studies
Male Fertility Study: Phase III in male volunteers or patients
Female Reproduction and Development Toxicity Studies:
Segment II studies in 2 species; Phase II, III involving female patients of child bearing age.
Segment I study; Phase III involving female patients of child-bearing age.
Segment III study; Phase III for drugs to be given to pregnant or nursing mothers for long periods or where there are indications of possible adverse effects on foetal development.
Allergenicity or Hypersensitivity:
Phase I, II, III - when there is a cause of concern or for parenteral drugs (including dermal application)
Photo-allergy or dermal photo-toxicity:
Phase I, II, III - if the drug or a metabolite is related to an agent causing photosensitivity or the nature of action suggests such a potential.
Genotoxicity:
In-vitro studies – Phase I
Both in-vitro and in-vivo - Phase II, III
Carcinogenicity:
Phase III - when there is a cause for concern, or when the drug is to be used for more than 6 months.

Abbreviations: d -day; **h**-hour; **I**, **II**, **III** - Phase of clinical trial;

Note: (1) Animal toxicity data generated in other countries may be accepted and may not be asked to be repeated or duplicated in India on a case to case basis depending upon the quality of data and the credentials of the laboratory where such data has been generated.

(2) Requirements for fixed dose combinations are given in clause 4 of this Schedule.

(1.9) Number of animals required for repeated-dose toxicity studies

14 to 28 days					84 to 182 days			
Group	Rodent (Rat)		Non-rodent (Dog or Monkey)		Rodent (Rat)		Non-rodent (Dog or Monkey)	
	Male	Female	Male	Female	Male	Female	Male	Female
Control	6 to10	6 to10	2 to3	2 to3	15 to30	15 to30	4 to6	4 to6
Low dose	6 to10	6 to10	2 to3	2 to3	15 to30	15 to30	4 to6	4 to6
Intermediat e dose	6 to10	6 to10	2 to3	2 to3	15 to30	15 to30	4 to6	4 to6
High dose	6to10	6 to10	2 to3	2 to3	15 to30	15 to30	4 to6	4 to6

(1.10) Laboratory parameters to be included in toxicity studies:

Haematological parameters			
Haemoglobin	Total Red Blood Cell count	Haematocrit	Reticulocyte

Total White Blood Cell count	Differential White Blood Cell Count	Platelet count	Terminal Bone Marrow Examination
Erythrocyte sedimentation rate (ESR) (Non-rodents only)	General Blood Picture: A Special mention of abnormaland immature cells should be made		
Coagulation parameters (Non-rodents only): Bleeding Time, coagulation Time, prothrombin time, Activated partial Thromboplastin Time			
Urinalysis Parameters			
Colour	Appearance	Specific Gravity	24 hours urinary output
Reaction(pH)	Albumin	Sugar	Acetone
Bile pigments	Urobilinogen	Occult Blood	
Microscopic examination of urinary sediment			
Blood Biochemical parameters			
Glucose	Cholesterol	Triglycerides	High density lipoproteins (HDL) cholesterol (Non-rodents only)
Low density lipoproteins (LDL)	Bilirubin	Serum glutamic pyruvic transaminase (SGPT) (Alanine aminotransferase (ALT)	Serum glutamic oxaloacetic transaminase (SGOT)
Cholesterol(Non-rodents only) Aspartate aminotransferase (AST)			
Alkaline Phosphatase (ALP)	GGT (Non-rodents only)	Blood urea Nitrogen	Creatinine

Total proteins	Albumin	Globulin (Calculated values)	Sodium
Potassium	Phosphorus	Calcium	
Gross and Microscopic Pathology			
Brain*: Cerebrum, Cerebellum, Midbrain	(Spinal cord)	Eye	(Middle Ear)
Thyroid	(Parathyroid)	Spleen	Thymus
Adrenal*	(Pancreas)	(Trachea)	Lung*
Heart*	Aorta	Oesophagus	Stomach
Duodenum	Jejunum	Terminal ileum	Colon
(Rectum)	Liver*	Kidney*	Urinary bladder
Epididymis	Testis*	Ovary	Uterus*
Skin	Mammary gland	Mesenteric lymph node	Skeletal muscle

* Organs marked with an asterisk should be weighed.

( ) Organs listed in parenthesis should be examined if indicated by the nature of the drug or observed effects.

Non-clinical toxicity testing and safety evaluation data of an Investigational New Drug (IND) needed for the conduct of different phases of clinical trials.

Note: Refer clause 2 of Second Schedule for essential features of study designs of the non-

clinical toxicity studies listed below.

For Phase I Clinical Trials:

Systemic Toxicity studies:-

(I) Single dose toxicitystudies

(II) Dose Ranging Studies

(III) Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure.

Male fertility study:

In-vitro genotoxicity tests, -

Relevant local toxicity studies with proposed route of clinical application (duration depending on proposed length of clinical exposure).

Allergenicity or Hypersensitivity tests (when there is a cause for concern or for parenteral drugs, including dermal application).

Photo-allergy or dermal photo-toxicity test (if the drug or a metabolite is related to anagent causing photosensitivity or the nature of action suggests such a potential).

For Phase II Clinical Trials: Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I trial, with appropriate references.

In case of an application for directly starting a Phase II trial - complete details of then on clinical safety data needed for obtaining the permission for Phase I trial, as per the list provided above must be submitted.

Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure.

In-vivo genotoxicity tests.

Segment II reproductive or developmental toxicity study (if female patients of child bearing

age are going to be involved).

For Phase III Clinical Trials: Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I and II trials, with appropriate references. In case of an application for directly initiating a Phase III trial - complete details of the non-clinical safety data needed for obtaining the permissions for Phase I and II trials, as per the list provided above must be provided.

Repeat-dose systemic toxicity studies of appropriate duration to support the duration of proposed human exposure.

Reproductive or developmental toxicity studies

Segment I (if female patients of child bearing age are going to be involved), and Segment III (for drugs to be given to pregnant or nursing mothers or where there are indications of possible adverse effects on foetal development).

Carcinogenicity studies (when there is a cause for concern or when the drug is to be used for more than 6 months).

For Phase IV Clinical Trials: Provide a summary of all the non-clinical safety data (listed above) already submitted while obtaining the permissions for Phase I, II and III trials, with appropriate references.

In case an application is made for initiating the Phase IV trial, complete details of the non-clinical safety data needed for obtaining the permissions for Phase I, II and III trials, as per the list provided above must be submitted.

Application of Good Laboratory Practices (GLP) -

The animal studies be conducted in an accredited laboratory. Where the safety pharmacology studies are part of toxicology studies, these studies should also be conducted in an accredited laboratory.

(2) The animal toxicology requirements as referred above should be viewed as general guidance for drug developments. Animal toxicology studies may be planned, designed and conducted as per the International Council of Harmonization (ICH) guidelines to promote safe, ethical development and availability of new drugs with reduced use of animals in accordance with the 3R (reduce/refine/replace) principles.

3. Animal Pharmacology.- *(1) General Principles***.-** Specific and general pharmacological studies should be conducted to support use of therapeutics in humans. In the early stages of drug development enough information may not be available to rationally select study design for safety assessment. In such a situation, a general approach to safety pharmacology studies can be applied. Safety pharmacology studies are studies that investigate potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure within the therapeutic range or above.

1.1 Specific pharmacological actions,- Specific pharmacological actions are those which demonstrate the therapeutic potential for humans.

The specific studies that should be conducted and their design will be different based on the individual properties and intended uses of investigational drug. Scientifically validated methods should be used. The use of new technologies and methodologies in accordance with sound scientific principles should be preferred.

1.2 General pharmacological actions,-

1.2.1 Essential safety pharmacology.- Safety pharmacology studies need to be conducted to investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure within the therapeutic range and above. These studies should be designed to identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety; to evaluate adverse pharmacodynamic or pathophysiological effects observed in toxicology or clinical studies; and to investigate the mechanism of the adverse pharmacodynamic effects observed or suspected. The aim of the essential safety pharmacology is to study the effects of the test drug on vital functions. Vital organ systems such as cardiovascular, respiratory and central nervous systems should be studied. Essential safety pharmacology studies may be excluded or supplemented based on scientific rationale. Also, the exclusion of certain tests or exploration(s) of certain organs, systems or functions should be scientifically justified.

1.2.1.1 Cardiovascular system: Effects of the investigational drug should be studied on blood pressure, heart rate, and the electrocardiogram. If possible in vitro, in vivo and/or ex vivo methods including electrophysiology should also be considered.

1.2.1.2 Central nervous system: Effects of the investigational drug should be studied on motor activity, behavioural changes, coordination, sensory and motor reflex responses and body temperature.

1.2.1.3 Respiratory system: Effects of the investigational drug on respiratory rate and other functions such as tidal volume and haemoglobin oxygen saturation should be studied.

1.3 Follow-up and supplemental safety pharmacology studies.- In addition to the essential safety pharmacological studies, additional supplemental and follow-up safety pharmacology studies may need to be conducted as appropriate. These depend on the pharmacological properties or chemical class of the test substance, and the data generated from safety pharmacology studies, clinical trials, pharmacovigilance, experimental in vitro or in vivo studies, or from literature reports.

1.3.1 Follow-up studies for essential safety pharmacology: Follow-up studies provide additional information or a better understanding than that provided by the essential safety pharmacology.

1.3.1.1 Cardiovascular system: These include ventricular contractility, vascular resistance and the effects of chemical mediators, their agonists and antagonists on the cardiovascular system.

1.3.1.2 Central nervous system: These include behavioural studies, learning and memory, electrophysiology studies, neurochemistry and ligand binding studies.

1.3.1.3 Respiratory system: These include airway resistance, compliance, pulmonary arterial pressure, blood gases and blood pH.

1.3.2 Supplemental safety pharmacology studies: These studies are required to investigate the possible adverse pharmacological effects that are not assessed in the essential safety pharmacological studies and are a cause for concern.

1.3.2.1 Urinary system: These include urine volume, specific gravity, osmolality, pH, proteins, cytology and blood urea nitrogen, creatinine and plasma proteins estimation.

1.3.2.2 Autonomic nervous system: These include binding to receptors relevant for the autonomic nervous system, and functional response to agonist or antagonist responses in vivo or in vitro, and effects of direct stimulation of autonomic nerves and their effects on cardiovascular responses.

1.3.2.3 Gastrointestinal system: These include studies on gastric secretion, gastric pH measurement, gastric mucosal examination, bile secretion, gastric emptying time in vivo and ileocaecal contraction in vitro.

1.3.2.4 Other organ systems: Effects of the investigational drug on organ systems not investigated elsewhere should be assessed when there is a cause for concern. For example, dependency potential, skeletal muscle, immune and endocrine functions may be investigated.

1.4 Conditions under which safety pharmacology studies are not necessary: Safety pharmacology studies are usually not required for locally applied agents e.g. dermal or ocular, in cases when the pharmacology of the investigational drug is well known, and/or when systemic absorption from the site of application is low. Safety pharmacology testing is also not necessary, in the case of a new derivative having similar pharmacokinetics and pharmacodynamics.

1.5 Timing of safety pharmacology studies in relation to clinical development :

1.5.1 Prior to first administration in humans: The effects of an investigational drug on the vital functions listed in the essential safety pharmacology should be studied prior to first administration in humans. Any follow-up or supplemental studies identified, should be conducted if necessary, based on a cause for concern.

1.5.2 During clinical development: Additional investigations may be warranted to clarify observed or suspected adverse effects in animals and humans during clinical development.

1.5.3 Before applying for marketing approval: Follow-up and supplemental safety pharmacology studies should be assessed prior to approval unless not required, in which case this should be justified. Available information from toxicology studies addressing safety pharmacology endpoints or information from clinical studies can replace such studies.

1.6 Application of Good Laboratory Practices (GLP): The animal studies be conducted in an accredited laboratory. Where the safety pharmacology studies are part of toxicology studies, these studies should also be conducted in an accredited laboratory.

4. Fixed Dose Combinations (FDCs). - Fixed dose combinations refer to products containing one or more active ingredients used for a particular indication. Fixed Dose Combinations (FDCs) can be divided into the following groups and data required for approval for marketing is described below:

(a) The first group of Fixed Dose Combinations (FDCs) includes those in which one or more of the active ingredients is a new drug. For such Fixed Dose Combinations (FDCs) to be approved for marketing data to be submitted will be similar to data required for any new drug (including clinical trials).

(b) (i) The second group Fixed Dose Combinations (FDCs) includes those in which active ingredients already approved or marketed individually are combined for the first time, for a particular claim and where the ingredients are likely to have significant interaction of a pharmacodynamic or pharmacokinetic nature. If clinical trials have been carried out with the Fixed Dose Combination (FDC) in other countries, reports of such trials should be submitted. If the Fixed Dose Combination (FDC) is marketed abroad, the regulatory status in other countries should be stated.

(ii) For marketing permission, appropriate chemical and pharmaceutical data will be submitted. In case such a combination is not marketed anywhere in the world but these drugs are already in use concomitantly (not as a Fixed Dose Combination (FDC) but individually) for the said claim, marketing permission may be granted based on chemical and pharmaceutical data. Data showing the stability of the proposed dosage form will also have to be submitted.

(iii) For any other such Fixed Dose Combinations (FDCs), clinical trials may be required. For obtaining permission to carry out clinical trials with such Fixed Dose Combinations (FDCs) a summary of available pharmacological, toxicological and clinical data on the individual ingredients should be submitted, along with the rationale for combining them in the proposed ratio. In addition, acute toxicity data (Lethal Dose 50 (LD 50)) and pharmacological data should be submitted on the individual ingredients as well as their combination in the proposed ratio.

(c) The third group of Fixed Dose Combinations (FDCs) includes those which are already marketed, but in which it is proposed either to change the ratio of active ingredients or to make a new therapeutic claim. For such Fixed Dose Combinations (FDCs), the appropriate rationale including published reports (if any) should be submitted to obtain marketing permission. Permission will be granted depending upon the nature of the claim and data submitted.

(d) The fourth group of Fixed Dose Combination (FDC) includes those whose individual active ingredients (or drugs from the same class) have been widely used in a particular indications for years, their concomitant use is often necessary and no claim is proposed to be made other than convenience. It will have to be demonstrated that the proposed dosage form is stable and the ingredients are unlikely to have significant interaction of a pharmacodynamic or pharmacokinetic nature. No additional animal or human data are generally required for these Fixed Dose Combinations (FDCs), and marketing permission may be granted if the Fixed Dose Combination (FDC) has an acceptable rationale.

5. Stability Testing of New Drugs. - Stability testing is to be performed to provide evidence on how the quality of a drug substance or formulation varies with time under the influence of various environmental factors such as temperature, humidity and light, and to establish shelf life for the formulation and recommended storage conditions.

Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety or efficacy. In case of formulations the testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system).

Validated stability-indicating analytical procedures should be applied. For long term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance.

In general, a drug substance should be evaluated under storage conditions that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the length of studies chosen should be sufficient to cover storage, shipment and subsequent use.

Stress testing of the drug substance should be conducted to identify the likely degradation products, which in turn establish the degradation pathways, evaluate the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of formulation involved.

Stress testing may generally be carried out on a single batch of the drug substance. It should include the effect of temperatures), humidity where appropriate, oxidation, and photolysis on the drug substance.

Data should be provided for

(a) Photostability on at least one primary batch of the drug substance as well as the formulation, as the case may be; and

(b) the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension.

Long-term testing should cover a minimum of six months duration if there is no significant change at any time during six months testing at accelerated storage condition or twelve months duration if there is significant changes in the six months accelerated stability testing on at least three primary batches of the drug substance or the formulation at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Accelerated testing should cover a minimum of six months duration at the time of submission.

In case of drug substances, the batches should be manufactured to a minimum of pilot scale by the same synthetic route and using a method of manufacture that simulates the final process to be used for production batches. In case of formulations, two of the three batches should be at least pilot scale and the third one may be smaller.

The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide products of the same quality and meeting the same specifications as that intended for marketing.

The stability studies for drug substances should be conducted either in the same container - closure system as proposed for storage and distribution or in a container - closure system that simulates the proposed final packaging. In case of formulations, the stability studies should be conducted in the final container - closure system proposed for marketing.

Stability testing of new drug substances and formulations:

(i)Study conditions for drug substances and formulations intended to be stored under general conditions

Study	*Study conditions*	*Duration of study*
Long-term	30°C ± 2° C/75% RH ± 5% RH	6 months or 12 months
Accelerated	40°C ± 2° C/75% RH ± 5% RH	6 months

(ii) If at any time during 6 months testing under the accelerated storage condition, such changes occur that cause the product to fail in complying with the prescribed standards, additional testing under an intermediate storage condition should be conducted and evaluated against significant change criteria.

(iii) Study conditions for drug substances and formulations intended to be stored in a refrigerator.

Study	*Study conditions*	*Duration of study*
Long-term	5°C ± 3° C	6 months or 12 months
Accelerated	25°C ± 2° C/60% RH ± 5%RH	6 months

(iv) Study conditions for drug substances and formulations intended to be stored in a freezer

Study	*Study conditions*	*Duration of study*
Study	Study conditions	Durations of study
Long-term	-20° C ± 5° C	6 months or 12 months

(v) Drug substances intended for storage below -20° C shall be treated on a case-by-case basis.

(vi) Stability testing of the formulations after constitution or dilution, if applicable, should be conducted to provide information for the labelling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in- use period.

TABLE 1

DATA TO BE SUBMITTED ALONG WITH THE APPLICATION TO CONDUCT CLINICAL TRIALS OR IMPORT OR MANUFACTURE OF NEW DRUGS FOR SALE IN THE COUNTRY

1. Introduction: A brief description of the drug and the therapeutic class to which it belongs.

2. Chemical and pharmaceutical information

2.1. Information on active ingredients.- Drug information (Generic Name, Chemical Name or International Nonproprietary Names (INN))

2.2. Physicochemical data.-

(a) Chemical name and Structure

Empirical formula

Molecular weight

(b) Physical properties

Description

Solubility

Rotation

Partition coefficient

Dissociation constant.

2.3. Analytical data

Elemental analysis

Mass spectrum

NMR spectra

IR spectra

UV spectra

Polymorphic identification.

2.4. Complete monograph specification including

Identification

Identity or quantification of impurities

Enantiomeric purity

Assay.

2.5. Validations

Assay method

Impurity estimation method

Residual solvent/other volatile impurities (OVI) estimation method.

2.6. Stability studies (for details refer clause 5 of this Schedule)

Final release specification

Reference standard characterization

Material safety data sheet.

2.7. Data on formulation

(i) Dosage form

(ii) Composition

(iii) Master manufacturing formula

(iv) Details of the formulation (including inactive ingredients)

(v) In process quality control check

(vi) Finished product specification

(vii) Excipient compatibility study

(viii) Validation of the analytical method

(ix) Comparative evaluation with international brand or approved Indian brands, if applicable.

(x) Pack presentation

(xi) Dissolution assay

(xii) Impurities

(xiii) Content uniformity pH

(xiv) Force degradation study

(xv) Stability evaluation in market intended pack at proposed storage conditions

(xvi) Packing specifications

(xvii) Process validation

When the application is for clinical trials only, the international non-proprietary name (INN) or generic name, drug category, dosage form and data supporting stability in the intended container-closure system for the duration of the clinical trial (information covered in item numbers 2.1, 2.3, 2.6, 2.7) are required.

3. Animal pharmacology (for details refer clause 3 of this Schedule)

3.1. Summary

3.2. Specific pharmacological actions

3.3. General pharmacological actions

3.4. Follow-up and supplemental safety pharmacology studies

3.5. Pharmacokinetics: absorption, distribution; metabolism; excretion

4. Animal toxicology (for details refer clause 2 of this Schedule)

4.1. General aspects

4.2. Systemic toxicity studies

4.3. Male fertility study

4.4. Female reproduction and developmental toxicity studies

4.5. Local toxicity

4.6. Allergenicity or Hypersensitivity

4.7. Genotoxicity

4.8. Carcinogenicity

Note: Where the data on animal toxicity as per the specifications of clause 2has been submitted and the same has been considered by the regulatory authority of the country which had earlier approved the drug, the animal toxicity studies shall not be required to be conducted in India except in cases where there are specific concerns recorded in writing.

5. Human or Clinical pharmacology (Phase I)

5.1. Summary

5.2. Specific Pharmacological effects

5.3. General Pharmacological effects

5.4. Pharmacokinetics, absorption, distribution, metabolism, excretion

5.5. Pharmacodynamics / early measurement of drug activity

6. Therapeutic exploratory trials (Phase II)

6.1. Summary

6.2. Study report as given in Table 6 of Third Schedule

7. Therapeutic confirmatory trials (Phase III)

7.1. Summary

7.2. Individual study reports with listing of sites and investigators.

8. Special studies

8.1. Summary

8.2. Bio-availability or Bio-equivalence.

8.3. Other studies e.g. geriatrics, paediatrics, pregnant or nursing women

9. Regulatory status in other countries

9.1. Countries where the drug is

(a) Marketed

(b) Approved

(c) Approved as Investigational New Drug (IND)

(d) Withdrawn, if any, with reasons

9.2. Restrictions on use, if any, in countries where marketed/approved

9.3. Free sale certificate or certificate of analysis, as appropriate.

10. Prescribing information

10.1. Proposed full prescribing information
10.2. Drafts of labels and cartons

11. Samples and Testing protocol/s

11.1. Samples of pure drug substance and finished product (an equivalent of 50 clinical doses, or more number of clinical doses if prescribed by the Central Licencing Authority), with testing protocols, full impurity profile and release specifications.

12. New chemical entity and Global clinical trial:

12.1Assessment of risk versus benefit to the patients
12.2Innovation vis-à-vis existing therapeutic option
12.3 Unmet medical need in the country.

13. Copy of license to manufacture any drug for sale granted by State Licencing Authority (in case the application is for manufacture for sale of new drug)

Note: (1) All items may not be applicable to all drugs. For explanation, refer text of this First Schedule, Second Schedule and Third Schedule.

(2) For requirements of data to be submitted with application for clinical trials refer text of the First Schedule, Second Schedule and Third Schedule.

TABLE 2
DATA REQUIRED TO BE SUBMITTED BY AN APPLICANT FOR GRANT OF PERMISSION TO IMPORT OR MANUFACTURE A NEW DRUG

ALREADY APPROVED IN THE COUNTRY

1. Introduction

A brief description of the drug and the therapeutic class

2. Chemical and pharmaceutical information

2.1 Chemical name, code name or number, if any; non-proprietary or generic name, if any, structure; physico-chemical properties

2.2 Dosage form and its composition

2.3 Test specifications

(a) active ingredients

(b) inactive ingredients

2.4 Tests for identification of the active ingredients and method of its assay

2.5 Specifications of finished product

2.6 Outline of the method of manufacture of active ingredient and finished product

2.7 Stability data

3. Marketing information

3.1 Proposed package insert or promotional literature

3.2 Draft specimen of the label and carton

4. Special studies conducted with approval of Central Licencing Authority

4.1 Bioavailability or Bioequivalence and comparative dissolution studies for oral dosage forms

4.2 Sub-acute animal toxicity studies for intravenous infusions and injectables.

TABLE 3

DATA REQUIRED TO BE SUBMITTED BY AN APPLICANT FOR CONDUCT OF CLINICAL TRIAL OF AN APPROVED NEW DRUG WITH NEW CLAIMS, NAMELY, NEW INDICATION OR NEW DOSAGE FORM OR NEW ROUTE OF ADMINISTRATION OR NEW STRENGTH OR TO IMPORT OR MANUFACTURE SUCH NEW DRUG FOR SALE OR DISTRIBUTION

1. Number and date of permission or license already granted for the approved new drug.
2. Therapeutic justification for new claim- new indication or modified dosage form/new route of administration

Chemical and Pharmaceutical information

3.1 Chemical name, code name or number, if any; non-proprietary or generic name, if any, structure; physico-chemical properties

3.2 Dosage form and its composition

3.3 Test specifications

(a) active ingredients

(b) inactive ingredients

3.4 Tests for identification of the active ingredients and method of its assay

3.5 Specifications of finished product

3.6 Outline of the method of manufacture of active ingredient and finished product

3.7 Stability data

4. Therapeutic justification for new claim or modified dosage form
5. Animal pharmacological and toxicological data as referred in clause 1, clause 2 and clause 3 of this Schedule.
6. Clinical trial data as referred in clause 1 of this Schedule.
7. Regulatory status in other countries
8. Marketing information:

8.1 Proposed package insert or promotional literature

8.2 Draft specimen of the label and carton

TABLE 4

DATA TO BE SUBMITTED ALONG WITH APPLICATION TO CONDUCT CLINICAL TRIAL OR IMPORT OR MANUFACTURE OF A PHYTOPHARMACEUTICAL DRUG IN THE COUNTRY

PART – A

1. Data to be submitted by the applicant:

1.1.A brief description or summary of the phyto pharmaceutical drug giving the botanical name of the plant (including vernacular or scriptural name, wherever applicable), formulation and route of administration, dosages, therapeutic class for which it is indicated and the claims to be made for the phytopharmaceutical product.

1.2.Published literature including information on plant or product or phytopharmaceutical drug, as a traditional medicine or as an ethno medicine and provide reference to books and other documents, regarding composition, process prescribed, dose or method of usage, proportion of the active ingredients in such traditional preparations per dose or per day's consumption and uses.

1.3.Information on any contraindications, side effects mentioned in traditional medicine or ethno medicine literature or reports on current usage of the formulation.

1.4.Published scientific reports in respect of safety and pharmacological studies relevant for the phytopharmaceutical drug intended to be marketed,-

(a) where the process and usages are similar or same to the product known in traditional medicine or ethno medicine; and

(b) where process or usage is different from that known in traditional medicine or ethno medicine.

1.5.Information on any contraindications, side effects mentioned or reported in any of the studies, information on side effects and adverse reactions reported during current usage of the phytopharmaceutical in the last three years, wherever applicable.

1.6.Present usage of the phytopharmaceutical drug - to establish history of usages, provide details of the product, manufacturer, quantum sold, extent of exposure on human population and number of years for which the product is being sold.

2. Human or clinical pharmacology information:

2.1.Published scientific reports in respect of pharmacological studies including human studies or clinical studies or epidemiological studies, relevant for the phytopharmaceutical drug intended to be marketed,-

(a) where the process and usages are similar or same to the product known in traditional medicine or ethno medicine; and

(b) where process or usage is different from that known in traditional medicine or ethno medicine.

2.2. Pharmacodynamic information (if available).

2.3.Monographs, if any, published on the plant or product or extract or phytopharmaceutical. (Copies of all publications, along with English translation to be attached.)

PART -B

DATA GENERATED BY APPLICANT

3. Identification, authentication and source of plant used for extraction and fractionation:

3.1 Taxonomical identity of the plant used as a source of the phytopharmaceutical drug giving botanical name of genus, species and family, followed by the authority citation (taxonomist's name who named the species), the variety or the cultivar (if any) needs to be mentioned.

3.2 Morphological and anatomical description giving diagnostic features and a photograph of the plant or plant part for further confirmation of identity and authenticity. (Furnish certificate of confirmation of botanical identity by a qualified taxonomist).

3.3 Natural habitat and geographical distribution of the plant and also mention whether the part of the plant used is renewable or destructive and the source whether cultivated or wild.

3.4 Season or time of collection.

3.5 Source of the plant including its geographical location and season or time of collection.

3.6 A statement indicating whether the species is any of the following, namely:-

(a) determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered species (CITES) of wild Fauna and Flora;

(b) entitled to special protection under the Biological Diversity Act, 2002 (18 of 2003);

(c) any known genotypic, chemotypic and ecotypic variability of species.

3.7. A list of grower or supplier (including names and addresses) and information on the following items for each grower or supplier, if available or identified already, including information of primary processing, namely: -

(a) harvest location;

(b) growth conditions;

(c) stage of plant growth at harvest;

(d) harvesting time;

(e) collection, washing, drying and storage conditions;

(f) handling, garbling and transportation;

(g) grinding, pulverising of the plant material; and

(h) sieving for getting uniform particle size of powdered plant material.

3.8. Quality specifications, namely:-

(a) foreign matter;

(b) total ash;

(c) acid insoluble ash;

(d) pesticide residue;

(e) heavy metal contamination;

(f) microbialload;

(g) chromatographic finger print profile with phytochemical reference marker;

(h) assay for bio-active or phytochemical compounds; and

(i) chromatographic fingerprint of a sample as per test method given under quality control of the phytopharmaceutical drug (photo documentation).

3.9 An undertaking to supply specimen sample of plant duly labelled and photocopy of the certificate of identity confirmation issued by a qualified taxonomist along with drawings or photographs of the diagnostic morphological and histological features of the botanical raw material used for the confirmation of authenticity.

4. Process for extraction and subsequent fractionation and purification:

4.1. Quality specifications and test methods for starting material.

4.2. Steps involved in processing.

(a) details of solvent used, extractive values, solvent residue tests or limits,

physico-chemical tests, microbial loads, heavy metal contaminants, chromatographic finger print profile with phytochemical reference markers, assay for active constituents or characteristic markers, if active constituents are not known;

(b) characterisation of final purified fraction;

(c) data on bio-active constituent of final purified fraction;

(d) information on any excipients or diluents or stabiliser or preservative used, if any.

4.3. Details of packaging of the purified and characterised final product, storage conditions and labelling.

5. Formulation of phytopharmaceutical drug applied for:

5.1. Details of the composition, proportion of the final purified fraction with defined markers of phytopharmaceutical drug per unit dose, name and proportions of all excipients, stabilisers and any other agent used and packaging materials.

5.2. Test for identification for the phytopharmaceutical drug.

5.3.Quality specifications for active and inactive phytopharmaceutical chromatographic finger print profile with phytochemical reference marker and assay of active constituent or characteristic chemical marker.

6. Manufacturing process of formulation:

6.1.The outline of the method of manufacture of the dosage form, along with environmental controls, in-process quality control tests and limits for acceptance.

6.2.Details of all packaging materials used, packing steps and description of the final packs.

6.3.Finished product's quality specifications, including tests specific for the dosage form, quality and chromatographic finger print profile with phytochemical reference marker and assay for active constituent or characteristic marker, if active constituents are not known.

7. Stability data:

7.1. Stability data of the phytopharmaceutical drug described at 4 above, stored at room temperature or 40+/- 2 deg. C and humidity at 75%RH +/-5%RHfor 0, 1, 2, 3 and 6 months.

7.2 Stability data of the phytopharmaceutical drug in dosage form or formulation stored at room temperature or 40 +/- 2 deg. C and humidity at 75%RH +/-5%RH for 0, 1, 2, 3 and 6 months, in the pack intended for marketing.

8. Safety and pharmacological information:

8.1. Data on safety and pharmacological studies to be provided.

8.2. Animal toxicity and safety data:

(a) 28 to 90 days repeat dose oral toxicity on two species of animals;

(b) In-vitro genotoxicity data (Ame's test and Chromosomal aberration test);

(c) dermal toxicity tests for topical use products;

(d) teratogenicity study (only if phytopharmaceutical drug is intended for use during pregnancy).

9. Human studies:

9.1.Clinical trials for phytopharmaceutical drugs to be conducted as per applicable Rules and guidelines for new drugs.

9.2.For all phytopharmaceutical drugs data from phase I (to determine maximum tolerated dose and associated toxicities) and the protocols shall be submitted prior to performing the studies.

9.3.Data of results of dose finding studies performed and the protocols shall be submitted prior to performing the studies:

Provided that in the case of phytopharmaceutical drug already marketed for more than five years or where there is adequate published evidence regarding the safety of the phytopharmaceutical drug, the studies may be abbreviated, modified or relaxed.

10. Confirmatory clinical trials:

10.1. Submit protocols for approval for any specific or special safety and efficacy study proposed specific to the phytopharmaceutical drug.

10.2. Submit proposed protocol for approval for human clinical studies appropriate to generate or validate safety and efficacy data for the phytopharmaceutical dosage form or product as per applicable Rules and guidelines.

10.3. Submit information on how the quality of the formulation would be maintained during the above studies.

11. Regulatory status:

11.1. Status of the phytopharmaceutical drug marketed in any country under any category like functional food or dietary supplement or as Traditional medicine or as an approved drug.

12. Marketing information:

12.1. Details of package insert or patient information sheet of the phytopharmaceutical drug to be marketed.

12.2. Draft of the text for label and carton.

13. Post marketing surveillance(PMS):

13.1. The applicant shall furnish periodic safety update reports every six months for the first two years after approval the drug is granted.

13.2. For subsequent two years the periodic safety update reports need to be submitted annually.

14. Any other relevant information:

Any other relevant information which the applicant considers that it will help in scientific evaluation of the application.

THIRD SCHEDULE

(See rules 8, 10, 11, 25, 35, 42 and 49)

CONDUCT OF CLINICAL TRIAL

1. Conduct of clinical trial.-

(i) Clinical trial shall be conducted in accordance with the provisions of the Act and these Rules and principles of Good Clinical Practice Guidelines.

(ii) Clinical trial on a new drug shall be initiated only after the permission has been granted by the Central Licencing Authority and the approval obtained from the respective ethics committee.

(iii)The Central Licencing Authority shall be informed of the approval of the respective institutional ethics committee in accordance with these rules.

(iv) All trial investigator should possess appropriate qualifications, training and experience and should have access to such investigational and treatment facilities as are relevant to the proposed trial protocol. A qualified physician (or dentist, when appropriate) who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions. Laboratories used for generating data for clinical trials should be compliant with good laboratory practices.

(v) Protocol amendments, if become necessary before initiation or during the course of a clinical trial, all such amendments should be submitted to the Central Licencing Authority in writing along with the approval by the ethics committee, if available, which has granted the approval for the study.

(vi) No deviations from or changes to the protocol should be implemented without prior written approval of the ethics committee and Central Licencing Authority except when it is necessary to eliminate immediate hazards to the trial subject or when change involves only logistic or administrative or minor aspects of the trial. All such exceptions must be immediately notified to the ethics committee as well as to the Central Licencing Authority. Administrative or logistic changes or minor amendments in the protocol should be notified to the Central Licencing Authority within thirty days.

2. Informed Consent.–

(a) In all trials, a freely given, informed, written consent is required to be obtained from each study subject. The Investigator must provide information about the study verbally as well as using a patient information sheet, in a language that is nontechnical and understandable by the study subject.

(b) The subject's consent must be obtained in writing using an "Informed Consent Form". Both the patient information sheet as well as the informed consent form should have been approved by the ethics committee and furnished to the Central Licencing Authority. Any changes in the informed consent documents should be approved by the ethics committee and submitted to the Central Licencing Authority before such changes are implemented.

(c) Where a subject is not able to give informed consent (e.g. an unconscious person or a minor or those suffering from severe mental illness or disability), the same may be obtained from a legally acceptable representative a legally acceptable representative is a person who is able to give consent for or authorise and intervention in the patient as provided by the law of India).

(d) If the trial subject his or her legally acceptable representative is unable to read or write an impartial witness should be present during the entire informed consent process who must append his or her signature to the consent form.

(e) In case of clinical trials on paediatrics, the subjects are legally unable to provide written informed consent, and are dependent on their parent or legal guardian to assume responsibility for their participation in clinical studies. In such case,-

(i) Written informed consent should be obtained from the parent or legal guardian. However, all paediatric participants should be informed to the fullest extent possible about the study in a language and in terms that they are able to understand.

(ii) Where appropriate, paediatric participants should additionally assent to enrol in the study. Mature minors and adolescents should personally sign and date a separately designed written assent form.

(iii)Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the Investigator and parent or legal guardian, the welfare of a paediatric patient would be jeopardized by his or her failing to participate in the study. In this situation, continued parental or legal guardian consent should be sufficient to allow participation in the study.

(f) A checklist of essential elements to be included in the study subject's informed consent document as well as a format for the informed consent form for trial subject is given in Table 3of this Schedule.

(g) An audio-video recording of the informed consent process in case of vulnerable subjects in clinical trials of New Chemical Entity or New Molecular Entity including procedure of providing information to the subject and his understanding on such consent, shall be maintained by the investigator for record:

Provided that in case of clinical trial of anti-HIV and anti-leprosy drugs, only audio recording of the informed consent process of individual subject including the procedure of providing information to the subject and his understanding on such consent shall be maintained by the investigator for record.

3.Responsibilities. -

(1) Sponsor.- (i) The clinical trial sponsor is responsible for implementing and maintaining quality assurance systems to ensure that the clinical trial is conducted and data generated, documented and reported in compliance with the protocol and Good Clinical Practices Guidelines as well as with all applicable statutory provisions. Standard operating procedures should be documented to ensure compliance with Good Clinical Practices Guidelines and applicable regulations.

(ii) Sponsors are required to submit a status report on the clinical trial to the Central Licencing Authority at the prescribed periodicity.

(iii) In case of studies prematurely discontinued for any reason including lack of commercial interest in pursuing the new drug application, a summary report should be submitted within 3 months. The summary report should provide a brief description of the study, the number of patients exposed to the drug, dose and duration of exposure, details of adverse drug reactions, if any, and the reason for discontinuation of the study or non-pursuit of the new drug application;

(iv)Any report of the serious adverse event, after due analysis shall be forwarded by the sponsor to the Central Licencing Authority, the Chairperson of the ethics committee and the head of the institution where the trial has been conducted, within fourteen days of knowledge of occurrence of the serious adverse event as specified in Table 5 of this Schedule;

(v) In case of injury or death occurring to the trial subject, the sponsor (whether a pharmaceutical company or an institution) or his representative or the investigator or the institution or centre where the study was conducted, as the case may be, shall make payment for medical management of the subject and also provide financial compensation for the clinical trial related injury or death in accordance with the procedure as prescribed in Chapter VI of these rules

(vi)The sponsor (whether a pharmaceutical company or an Institution) or his representative, whosoever had obtained permission from the Central Licencing Authority for conduct of the clinical trial, shall submit details of compensation provided or paid for clinical trial related injury or death, to the Central Licencing Authority thirty days of the receipt of the order of the Central Licencing Authority.

(vii) The sponsor shall provide post-trial access of the investigational drug by giving the drug free of cost to the trial subject as per directions of the Central Licencing Authority in special circumstances on the recommendations of the investigator and the ethics committee and written consent of the patient in accordance with rule 27.

(2) Investigator.- (i) The investigator shall be responsible for the conduct of the trial according to the protocol and the Good Clinical Practices Guidelines and also for compliance as per the undertaking given in Table 4. Standard operating procedures are required to be documented by the investigators for the tasks performed by them.

(i) During and following a subject's participation in trial, the investigator should ensure that adequate medical care is provided to the participant for any adverse events.

(ii) Investigator shall report all serious adverse events to the Central Licencing Authority, the sponsor or his representative, whosoever had obtained permission from the Central Licencing Authority for conduct of the clinical trial, and the ethics committee that accorded approval to the study protocol, within twenty-four hours of their occurrence.

(iv) In case, the investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reason for the delay to the satisfaction of the Central Licencing Authority along with the report of the serious adverse event. The report of the serious adverse event, after due analysis, shall be forwarded by the investigator to the Central Licencing Authority, the Chairperson of the ethics committee and the Head of the institution where the trial has been conducted within fourteen days of the occurrence of the serious adverse event.

(v) The investigator shall provide information to the trial subject through informed consent process as provided in Table 3about the essential elements of the clinical trial and the subject's right to claim compensation in case of trial related injury or death. He shall also inform the subject his or her nominee of their rights to contact the sponsor or his representative whosoever had obtained permission from the Central Licencing Authority for conduct of the clinical trial for the purpose of making claims in the case of trial related injury or death.

(3) Ethics committee.-

(i) It is the responsibility of the ethics committee that reviews and accords its approval to a trial protocol to safeguard the rights, safety and well-being of all trial subjects.

(ii) The ethics committee should exercise particular care to protect the rights, safety and well-being of all vulnerable subjects participating in the study, e.g., members of a group with hierarchical structure (e.g. prisoners armed forces personnel, staff and students of medical, nursing and pharmacy academic institutions), patients with incurable diseases, unemployed or impoverished persons, patients in emergency situation, ethnic minority groups, homeless persons, nomads, refugees, minors or other incapable of personally giving consent.

(iii) Ethics committee should get documented "standard operating procedures' and should maintain a record of its proceedings.

(iv) Ethics committee should make, at appropriate intervals, an ongoing review of the trials for which they have reviewed the protocol. Such a review may be based on the periodic study progress reports furnished by the investigators or monitoring and internal audit reports furnished by the sponsor or visiting the study sites.

(v) In case an ethics committee revokes its approval accorded to a trial protocol, it must record the reasons for doing so and at once communicate such a decision to the Investigator as well as to the Central Licencing Authority.

(vi) In case of serious adverse event occurring to the trial subject, the ethics committee shall forward its report or order on the event, after due analysis, along with its opinion on the financial compensation, if any, to be paid by the sponsor or his representative or institution or centre, as the case may be, in accordance with Chapter VI of these rules.

TABLE 1

INFORMATION TO BE SUBMITTED BY AN APPLICANT FOR GRANT OF REGISTRATION OF ETHICS COMMITTEE AND FORMAT FOR ACCORDING APPROVAL

(A) Information required to be submitted by the applicant for registration of ethics committee:

(a) Name of the ethics committee.

(b) Authority under which the ethics committee has been constituted, membership requirements, the term of reference, conditions of appointment and the quorum required.

(c) The procedure for resignation, replacement or removal of members.

(d) Address of the office of the ethics committee.

(e) Name, address, qualification, organisational title, telephone number, fax number, email, mailing address and brief profile of the Chairperson.

(f) Names, qualifications, organisational title, telephone number, fax number, e-mail and mailing address of the members of the ethics committee. The information shall also include member's specialty (primary, scientific or non-scientific), member's affiliation with institutions and patient group representation, if any.

(g) Details of the supporting staff.

(h) The standard operating procedures to be followed by the committee in general.

(i) Standard operating procedures to be followed by the committee for vulnerable population

(j) Policy regarding training for new and existing committee members along with standard operating procedures.

(k) Policy to monitor or prevent the conflict of interest along with standard operating procedures.

(l) If the committee has been audited or inspected before, give details.

(B) Format for according approval to clinical trial protocol by the ethics committee

To

Dr.

Dear Dr._____

The Institutional ethics committee or independent ethics committee (state name of the committee, as appropriate) reviewed and discussed your application to conduct the clinical trial entitled "…….. "on…….(date).
The following documents were reviewed:

(a) Trial protocol (including protocol amendments), dated…….version No.(s) ……

(b) Patient information sheet and informed consent form (including updates, if any) in English or vernacular language.

(c) Investigator's brochure, dated..... , Version no…… Proposed methods for patient accrual including advertisements etc. proposed to be used for the purpose.

(d) Principal investigator's current Curriculum Vitae.

(e) Insurance policy or compensation for participation and for serious adverse events occurring during the study participation.

(f) Investigator's agreement with the sponsor.

(g) Investigator's undertaking (Table 4).

The following members of the ethics committee were present at the meeting held on (date, time, place).

……Chairperson of the ethics committee;

…….Member-Secretary of the ethics committee;

……..Name of each member with designation;

We approve the trial to be conducted in its presented form.

The ethics committee to be informed about the progress of the study, any Serious Adverse Events (SAE) occurring in the course of the study, any changes in the protocol and patient information or informed consent and to be provided with a copy of the final report.

Yours sincerely,

Member Secretary, Ethics Committee

TABLE 2

CONTENTS OF THE PROPOSED PROTOCOL FOR CONDUCTING CLINICAL TRIALS

Title Page

(a) Full title of the clinical study,

(b) Protocol, Study number, and protocol version number with date.

(c) The Investigational New Drug (IND) name/number of the investigational drug.

(d) Complete name and address of the Sponsor and contract research organization if any. (e) List of the investigators who are conducting the study, their respective institutional

affiliations and site locations

(f) Name of clinical laboratories and other departments and/or facilities participating in thestudy.

Table of Contents

1. Background and introduction

(a) Preclinical experience

(b) Clinical experience

Previous clinical work with the new drug should be reviewed here and a description of how the current protocol extends existing data should be provided. If this is an entirely new indication, how this drug was considered for this should be discussed. Relevant information regarding pharmacological, toxicological and other biological properties of the drug/biologic/medical device, and previous efficacy and safety experience should be described.

2. Study rationale: This section should describe a brief summary of the background information relevant to the study design and protocol methodology. The reasons for performing this study in the particular population included by the protocol should be provided.

3. Study objective (primary as well as secondary) and their logical relation to the study design.

4. Study design-

(a) Overview of the study design: Including a description of the type of study (i.e., double-blind, multicentre, placebo controlled, etc.), a detail of the specific treatment groups and number of study Subjects in each group and investigative site, Subject number assignment, and the type, sequence and duration of study periods.

(b) Flow chart of the study

(c) A brief description of the methods and procedures to be used during the study.

(d) Discussion of study design: This discussion details the rationale for the design chosen for this study.

5. Study population: the number of subjects required to be enrolled in the study at the investigative site and by all sites along with a brief description of the nature of the subject population required is also mentioned.

6. Subject eligibility

(a) Inclusion criteria

(b) Exclusion criteria

7. Study assessments - plan, procedures and methods to be described in detail.

8. Study conduct stating the types of study activities that would be included in this section would be: medical history, type of physical examination, blood or urine testing, electrocardiogram (ECG), diagnostic testing such as pulmonary function tests, symptom measurement, dispensation and retrieval of medication, Subject cohort assignment, adverse event review, etc.

Each visit should be described separately as Visit 1, Visit 2, etc.

Discontinued subjects: Describes the circumstances for Subject withdrawal, dropouts, or other reasons for discontinuation of Subjects. State how drop outs would be managed and if they would be replaced describe the method of handling of protocol waivers, if any. The person who approves all such waivers should be identified and the criteria used for specific waivers should be provided.

Describes how protocol violations will be treated, including conditions where the study will be terminated for noncompliance with the protocol.

9. Study treatment-

(a) Dosing schedule (dose, frequency, and duration of the experimental treatment) Describe the administration of placebos and/or dummy medications if they are part of the treatment plan. If applicable, concomitant drug(s), their doses, frequency, and duration of concomitant treatment should be stated.

(b) Study drug supplies and administration: A statement about who is going to provide the study medication and that the investigational drug formulation has been manufactured following all regulations Details of the product stability, storage requirements and dispensing requirements should be provided.

(c) Dose modification for study drug toxicity: Rules for changing the dose or stopping the study drug should be provided.

(d) Possible drug interactions

(e) Concomitant therapy: The drugs that are permitted during the study and the conditions under which they may be used are detailed here. Describe the drugs that a Subject is not allowed to use during parts of or the entire study. If any washout periods for prohibited medications are needed prior to enrolment, these should be described here.

(f) Blinding procedures: A detailed description of the blinding procedure if the study employs a blind on the Investigator and/or the Subject

(g) Un-blinding procedures: If the study is blinded, the circumstances in which un-blinding may be done and the mechanism to be used for un-blinding should be given

10. Adverse Events:

Description of expected adverse events should be given.

Procedures used to evaluate an adverse event should be described.

11. Ethical considerations: Give the summary of:

(a) Risk/benefit assessment:

(b) Ethics committee review and communications

(c) Informed consent process

(d) Statement of subject confidentiality including ownership of data and coding procedures.

12. Study monitoring and supervision:

A description of study monitoring policies and procedures should be provided along with the proposed frequency of site monitoring visits, and who is expected to perform monitoring.

Case Record Form (CRF) completion requirements, including who gets which copies of the forms and any specific required in filling out the forms Case Record Form correction requirements, including who is authorized to make corrections on the Case Record Form and how queries about study data are handled and how errors, if any, are to be corrected should be stated.

Investigator study files, including what needs to be stored following study completion should be described.

13. Investigational Product Management:

(a) Give investigational product description and packaging (stating all ingredients and the formulation of the investigational drug and any placebos used in the study)

(b) The precise dosing required during the study

(c) Method of packaging, labelling, and blinding of study substances

(d) Method of assigning treatments to subjects and the subject identification code numbering system

(e) Storage conditions for study substances

(f) Investigational product accountability: Describe instructions for the receipt, storage, dispensation, and return of the investigational products to ensure a complete accounting of all investigational products received, dispensed, and returned or destroyed.

(g) Describe policy and procedure for handling unused investigational products.

14. Data Analysis: Provide details of the statistical approach to be followed including sample size, how the sample size was determined, including assumptions made in making this determination, efficacy endpoints (primary as well as secondary) and safety endpoints.

Statistical analysis: Give complete details of how the results will be analysed and reported along with the description of statistical tests to be used to analyse the primary and secondary endpoints defined above. Describe the level of significance, statistical tests to be used, and the methods used for missing data; method of evaluation of the data for treatment failures, non-compliance, and Subject withdrawals; rationale and conditions for any interim analysis if planned.

Describe statistical considerations for Pharmacokinetic (PK) analysis, if applicable.

15. Undertaking by the Investigator (see Table 4)

16. Appendices: Provide a study synopsis, copies of the informed consent documents (patient information sheet, informed consent form etc.); Case Record Form (CRF) and other data collection forms; a summary of relevant pre-clinical safety information and any other documents referenced in the clinical protocol.

TABLE 3

INFORMED CONSENT

1. Checklist of informed consent documents for clinical trial subject,-

1.1 Essential elements:

(i) Statement that the study involves research and explanation of the purpose of the research.

(ii) Expected duration of the participation of subject.

(iii) Description of the procedures to be followed, including all invasive procedures.

(iv) Description of any reasonably foreseeable risks or discomforts to the Subject.

(v) Description of any benefits to the Subject or others reasonably expected from research. If no benefit is expected Subject should be made aware of this.

(vi) Disclosure of specific appropriate alternative procedures or therapies available to the Subject.

(vii) Statement describing the extent to which confidentiality of records identifying the Subject will be maintained and who will have access to Subject's medical records.

(viii) Trial treatment schedule and the probability for random assignment to each treatment (for randomized trials).

(ix) Statement describing the financial compensation and the medical management as under:

(a) In case of an injury occurring to the subject during the clinical trial, free medical management shall be given as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier.

(b) In the event of a trial related injury or death, the sponsor or his representative or the investigator or centre, as the case may be, in accordance with the rule 39, as the case may be, shall provide financial compensation for the injury or death.

(x)An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury.

(xi) The anticipated prorated payment, if any, to the subject for participating in the trial.

(xii) Responsibilities of subject on participation in the trial.

(xiii) Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the subject is otherwise entitled.

(xiv) Statement that there is a possibility of failure of investigational product to provide intended therapeutic effect.

(xv) Statement that in the case of placebo controlled trial, the placebo administered to the subjects shall not have any therapeutic effect.

(xvi) Any other pertinent information.

1.2 Additional elements, which may be required:

(a) Statement of foreseeable circumstances under which the participation of the subject may be terminated by the Investigator without his or her consent.

(b) Additional costs to the subject that may result from participation in the study.

(c) The consequences of a Subject's decision to withdraw from the research and procedures for orderly termination of participation by Subject.

(d) (d) Statement that the Subject or Subject's representative will be notified in a timely manner if significant new findings develop during the course of the research which may affect the Subject's willingness to continue participation will be provided.

(e). A statement that the particular treatment or procedure may involve risks to the Subject (or to the embryo or foetus, if the Subject is or may become pregnant), which are currently unforeseeable.

(f) Approximate number of Subjects enrolled in the study.

2. Format of informed consent form for Subjects participating in a clinical trial –

Informed Consent form to participate in a clinical trial

Study Title:

Study Number:

Subject's Initials: _____ Subject's Name:_____

Date of Birth/Age: _____

Address of the Subject ___

Qualification _____

Occupation: Student or Self-Employed or Service or Housewife or Others (Please click as appropriate) .

Annual Income of the subject:

Name and address of the nominees and his relation to the subject (for the purpose of compensation in case of trial related death).

		Place Initial box (Subject)
(i)	I confirm that I have read and understood the information Sheet dated _____ for the above study and have had the opportunity to ask questions.	[ ]
(ii)	I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	[ ]
(iii)	I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.	[ ]
(iv)	I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purposes	[ ]
(v)	I agree to take part in the above study.	[ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:

Date: _____/ ____ /

Signatory's Name: _____

Signature of the Investigator: _____ Date: ____ / ____ /

Study Investigator's Name: ___ _____

Signature of the Witness_____ Date: ____ / ____ /

Name of the Witness:_____

Copy of the Patient Information Sheet and duly filled Informed Consent Form shall be handed over to the subject his or her attendant.

TABLE 4

UNDERTAKING BY THE INVESTIGATOR

1. Full name, address and title of the Principal Investigator (or Investigators when there is no Principal Investigator).
2. Name and address of the medical college, hospital or other facility where the clinical trial will be conducted: Education, training & experience that qualify the Investigator for the clinical trial (Attach details including Medical Council registration number, or any other statements of qualifications)
3. Name and address of all clinical laboratory facilities to be used in the study.
4. Name and address of the Ethics Committee that is responsible for approval and continuing review of the study.
5. Names of the other members of the research team (Co-or sub-Investigators) who will be assisting the Investigator in the conduct of the investigations.
6. Protocol Title and Study number (if any) of the clinical trial to be conducted by the Investigator.
7. Commitments:

(i) I have reviewed the clinical protocol and agree that it contains all the necessary information to conduct the study. I will not begin the study until all necessary ethics committee and regulatory approvals have been obtained.

(ii) I agree to conduct the study in accordance with the current protocol. I will not implement any deviation from or changes of the protocol without agreement by the Sponsor and prior review and documented approval or favourable opinion from the ethics committee of the amendment, except where necessary to eliminate an immediate hazard to the trial subject or when the changes involved are only logistical or administrative in nature.

(iii) I agree to personally conduct or supervise the clinical trial at my site.

(iv) I agree to inform all trial subject, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent and ethics committee review and approval specified in the New Drugs and Clinical Trials Rules, 2019 and Good Clinical Practices guidelines are met.

(v) I agree to report to the Sponsor all adverse experiences that occur in the course of the investigation(s) in accordance with the regulatory requirements and Good Clinical Practices guidelines.

(vi) I have read and understood the information in the Investigator's brochure, including the potential risks and side effects of the drug.

(vii) I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are suitably qualified and experienced and they have been informed about their obligations in meeting their commitments in the trial.

(viii) I agree to maintain adequate and accurate records and to make those records available for audit or inspection by the Sponsor, ethics committee, Central Licencing Authority or their authorised representatives, in accordance with regulatory provisions and the Good Clinical Practices guidelines. I will fully cooperate with any study related audit conducted by regulatory officials or authorised representatives of the Sponsor.

(ix) I agree to promptly report to the ethics committee all changes in the clinical trial activities and all unanticipated problems involving risks to human subjects or others.

(x) I agree to inform all serious adverse events to the Central Licencing Authority, sponsor as well as the ethics committee within twenty-four hours of their occurrence. In case, of failure to do so, I shall furnish the reason for the delay to the satisfaction of the Central Licencing Authority along with the report of the serious adverse event.

(xi) The report of the serious adverse event, after due analysis, shall also be forwarded by me to the Central Licencing Authority, the Chairperson of the ethics committee and the Head of the institution where the trial has been conducted within fourteen days in accordance with the regulatory requirements.

(xii) I will maintain confidentiality of the identification of all participating subjects and assure security and confidentiality of study data.

(xiii) I agree to comply with all other requirements, guidelines and statutory obligations as applicable to clinical Investigators participating in clinical trials.

8. Signature of Investigator with date.

TABLE 5

DATA ELEMENTS FOR REPORTING SERIOUS ADVERSE EVENTS OCCURRING IN A CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY

1. Patient Details:

Initials and other relevant identifier (hospital or out-patient department (OPD) record number etc)*

Gender

Age or date of birth

Weight

Height

2. Suspected Drug(s) :

Generic name of the drug*

Indication(s) for which suspect drug was prescribed or tested.

Dosage form and strength.

Daily dose and regimen (specify units - e.g., mg, ml, mg/kg).

Route of administration.

Starting date and time of day.

Stopping date and time, or duration of treatment

3. Other Treatment(s):

Provide the same information for concomitant drugs (including non-prescription or Over the Counter OTC drugs) and non-drug therapies, as for the suspected drug(s).

4. Details of Serious Adverse Event :

Full description of the event including body site and severity, as well as the criterion (or criteria) for considering the report as serious. In addition to a description of the reported signs and symptoms, whenever possible, describe a specific diagnosis for the event*

Start date (and time) of onset of event.

Stop date (and time) or duration of event.

Dechallenge and rechallenge information.

Setting (e.g., hospital, out-patient clinic, home, nursing home).

5. Outcome

Information on recovery and any sequelae; results of specific tests or treatment that may have been conducted.

For a fatal outcome, cause of death and a comment on its possible relationship to the suspected event; Any post-mortem findings.

Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations etc.

6. Details about the Investigator*

Name and Address

Telephone number

Profession (specialty)

Date of reporting the event to Central Licencing Authority:

Date of reporting the event to ethics committee overseeing the site:

Signature of the Investigator or Sponsor

Note: Information marked * must be provided.

TABLE 6

STRUCTURE, CONTENT AND FORMAT FOR CLINICAL TRIAL REPORT

1. Title Page: This page should contain information about the title of the study, the protocol code, name of the investigational product tested, development Phase, indication studied, a brief description of the trial design, the start and end date of patient accrual and the names of the Sponsor and the participating Institutes (Investigators).

2. Study Synopsis (1 to 2 pages): A brief overview of the study from the protocol development to the trial closure should be given here. This section will only summarise the important conclusions derived from the study.

3. Statement of compliance with the Good Clinical Practices Guidelines.

4. List of abbreviations and definitions

5. Table of contents

6. Ethics Committee: This section should document that the study was conducted in accordance with the ethical principles of Declaration of Helsinki. A detailed description of the Ethics Committee constitution and dates of approvals of trial documents for each of the participating sites should be provided. A declaration should state that Ethics Committee (EC) notifications as per Good Clinical Practice Guidelines and Ethical Guidelines for Biomedical Research on Human Subjects, issued by Indian Council of Medical Research have been followed.

7. Study Team: Briefly describe the administrative structure of the study (Investigators, site staff, Sponsor or designates, Central laboratory etc.).

8. Introduction: A brief description of the product development rationale should be given here.

9. Study Objective: A statement describing the overall purpose of the study and the primary and secondary objectives to be achieved should be mentioned here.

10. Investigational Plan: This section should describe the overall trial design, the Subject selection criteria, the treatment procedures, blinding or randomisation techniques if any, allowed or disallowed concomitant treatment, the efficacy and safety criteria assessed, the data quality assurance procedures and the statistical methods planned for the analysis of the data obtained.

11. Trial Subjects: A clear accounting of all trial Subjects who entered the study will be given here. Mention should also be made of all cases that were dropouts or protocol deviations. Enumerate the patients screened, randomised, and prematurely discontinued. State reasons for premature discontinuation of therapy in each applicable case.

12. Efficacy evaluation: The results of evaluation of all the efficacy variables will be described in this section with appropriate tabular and graphical representation. A brief description of the demographic characteristics of the trial patients should also be provided along with a listing of patients and observations excluded from efficacy analysis.

13. Safety Evaluation: This section should include the complete list

13.1 all serious adverse events, whether expected or unexpected and

13.2 unexpected adverse events whether serious or not (compiled from data received as per Table 5 of this Schedule).

The comparison of adverse events across study groups may be presented in a tabular or graphical form. This section should also give a brief narrative of all important events considered related to the investigational product.

14 Discussion and overall Conclusion: Discussion of the important conclusions derived from the trial and scope for further development.

15. List of References:

16. Appendices: List of Appendices to the Clinical Study Report

(a) Protocol and amendments

(b) Specimen of Case Record Form

(c) Investigators' names with contact addresses, phone, e-mail etc.

(d) Patient data listings

(e) List of trial participants treated with investigational product

(f) Discontinued participants

(g) Protocol deviations

(h) Case Record Forms of cases involving death and life threatening adverse event cases

(i) Publications from the trial

(j) Important publications referenced in the study

(k) Audit certificate, if available

(l) Investigator' certificate that he/she has read the report and that the report accurately describes the conduct and the results of the study.

TABLE 7

INVESTIGATOR'S BROCHURE

The Investigator's Brochure should contain the version number, release date along with the following sections, each with literature references where appropriate:

1 Table of Contents

2 Summary: A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

3 Introduction: A brief introductory statement should be provided that contains the chemical name (and generic and trade name when approved) of the investigational product, all active ingredients, the investigational product pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product, and the anticipated prophylactic, therapeutic, or diagnostic indication. Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

4 Physical, Chemical, and Pharmaceutical Properties and Formulation: A description should be provided of the investigational product substance (including the chemical or structural formula), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties. To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form should also be given. Any structural similarities to other known compounds should be mentioned.

5 Nonclinical Studies

5.1 Introduction: The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in human. The information provided may include the following, as appropriate, if known or available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution

- Duration of post-exposure follow-up
- Results, including the following aspects:
  - Nature and frequency of pharmacological or toxic effects
  - Severity or intensity of pharmacological or toxic effects
  - Time to onset of effects
  - Reversibility of effects
  - Duration of effects
  - Dose response

Tabular format or listings should be used whenever possible to enhance the clarity of the presentation. The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) Nonclinical Pharmacology: A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) Pharmacokinetics and Product Metabolism in Animals: A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) Toxicology: A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose
- Repeated dose
- Carcinogenicity
- Special studies (e.g. irritancy and sensitization)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

6 Effects in Humans: (a) A thorough discussion of the known effects of the investigational products in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational products other than from in clinical trials, such as from experience during marketing.

(b) Pharmacokinetics and Product Metabolism in Humans

A summary of information on the pharmacokinetics of the investigational products should be presented, including the following, if available:

- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
- Bioavailability of the investigational product (absolute, where possible, or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food).
- Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

(c) Safety and Efficacy: A summary of information should be provided about the investigational product's or products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of

summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed. The Investigators Brochure IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the products.

(d) Marketing Experience: The Investigator's Brochure should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The Investigator's Brochure should also identify all the countries where the investigational product did not receive approval or registration for marketing or was withdrawn from marketing or registration.

7 Summary of Data and Guidance for the Investigator: This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational products, wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials. The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational products. Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug a reaction that is based on previous human experience and on the pharmacology of the investigational product.

TABLE 8

PRESCRIBING INFORMATION

1. Generic Name
2. Qualitative and quantitative composition
3. Dosage form and strength
4. Clinical particulars
   - 4.1 Therapeutic indication
   - 4.2 Posology and method of administration
   - 4.3 Contraindications
   - 4.4 Special warnings and precautions for use
   - 4.5 Drugs interactions
   - 4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)
   - 4.7 Effects on ability to drive and use machines
   - 4.8 Undesirable effects
   - 4.9 Overdose
5. Pharmacological properties
   - 5.1 Mechanism of Action
   - 5.2Pharmacodynamicproperties
   - 5.3 Pharmacokinetic properties
6. Nonclinical properties
   - 6.1 Animal Toxicology or Pharmacology
7. Description
8. Pharmaceutical particulars
   - 8.1 Incompatibilities
   - 8.2 Shelf-life

8.3 Packaging information

8.4 Storage and handing instructions

9. Patient Counselling Information

10. Details of manufacturer

11. Details of permission or licence number with date

12. Date of revision

FOURTH SCHEDULE

(See rules 33, 45, 48, 49 and 52)

REQUIREMENTS AND GUIDELINES FOR CONDUCT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDY OF NEW DRUGS OR INVESTIGATIONAL NEW DRUGS

1. General Principles: (1) Bioavailability or Bioequivalence focus on the release of an active drug from its dosage form and subsequent absorption into the systemic circulation. Bioavailability or Bioequivalence study of a pharmaceutical formulation is one of the components to ensure efficacy and safety of pharmaceutical product.

(2) Bioavailability can be generally documented by a systemic exposure profile obtained by measuring drug or metabolite concentration in the systemic circulation overtime.

(3) Bioequivalence study is conducted to ensure therapeutic equivalence between two pharmaceutically equivalent test product and a reference product.

(4) Bioavailability or Bioequivalence study is conducted to ensure therapeutic equivalence between an approved new drug formulation and reference product for subsequent applicant.

(5) Bioavailability or Bioequivalence study is also conducted to ensure therapeutic equivalence at any phase of clinical trial of a new chemical entity for establishing bioequivalence between two products of the chemical entity, which is important for certain pharmaceutical formulation or manufacturing changes occurring during the drug development stages.

(6) For drugs approved elsewhere in the world and absorbed systemically, bioequivalence with the reference formulation should be carried out wherever applicable. These studies should be conducted under the labelled conditions of administration. Data on the extent of systemic absorption may be required for formulations other than those designed for systemic absorption.

(7) Evaluation of the effect of food on absorption following oral administration should be carried out. Data from dissolution studies should also be submitted for all solid oral dosage forms.

(8) Dissolution and bioavailability data submitted with the new drug application must provide information that assures bioequivalence or establishes bioavailability and dosage correlations between the formulations sought to be marketed and those used for clinical trials during clinical development of the product.

(9) All bioavailability and bioequivalence studies should be conducted according to the Guidelines for Bioavailability and Bioequivalence studies issued by Central Drugs Standard Control Organisation, Ministry of Health and Family Welfare.

(10) Bioavailability and bioequivalence studies of a new drug or investigational new drug shall be conducted in a bioavailability and bioequivalence study centre registered under rule 47 after obtaining permission from the Central Licencing Authority.

2. Bioavailability and bioequivalence study centre:

2.1 The Bioavailability and bioequivalence study centre shall have following facilities for conducting bioavailability and bioequivalence study of any new drug or investigational new drug:

(2.1.1) Legal Identity: The organization, conducting the bioavailability or bioequivalence studies, or the parent organization to which it belongs, must be a legally constituted body with appropriate statutory registrations.

(2.1.2) Impartiality, confidentiality, independence and integrity: The organization shall:

(a) have managerial staff with the authority and the resources needed to discharge their duties.

(b) have arrangements to ensure that its personnel are free from any commercial, financial and other pressures which might adversely affect the quality of their work.

(c) be organised in such a way that confidence in its independence of judgment and integrity is maintained at all times.

(d) have documented policies and procedures, where relevant, to ensure the protection of its sponsors' confidential information and proprietary rights.

(e) not engage in any activity that may jeopardize the trust in its independence of judgment and integrity

(f) have documented policies and procedures for protection of rights, safety and well -being of study subject in consistent with the Provisions of the Drugs and Cosmetics Act and these Rules and Good Clinical Practices Guidelines

(g) have documented policies and procedures for scientific integrity including procedures dealing with and reporting possible scientific misconduct.

(2.1.3) Organisation and management: The study centre must include the following:

(a) An Investigator who has the overall responsibility to provide protection for safety of the study subject. The Investigator(s) should possess appropriate medical qualifications and relevant experience for conducting pharmacokinetic studies.

(b) The site should have facilities and identified adequately qualified and trained personnel to perform the following functions:

(i) Clinical Pharmacological Unit (CPU) management

(ii) Analytical laboratory management

(iii) Data handling and interpretation

(iv) Documentation and report preparation

(v) Quality assurance of all operations in the centre

(2.1.4) Documented Standard Operating Procedures: (1) The center shall establish and maintain a quality system appropriate to the type, range and volume of its activities. All operations at the site must be conducted as per the authorised and documented standard operating procedures.

(2) These documented procedures should be available to the respective personnel for ready reference. The procedures covered must include those that ensure compliance with all aspects of provision of the Act and these rules, good clinical practices guidelines and good laboratory practice guidelines.

(3) A partial list of procedures for which documented standard operating procedures should be available includes:

(a) maintenance of working standards (pure substances) and respective documentation;

(b) withdrawal, storage and handling of biological samples;

(c) maintenance, calibration and validation of instruments;

(d) managing medical as well as non-medical emergency situations;

(e) handling of biological fluids;

(f) managing laboratory hazards;

(g) disposal procedures for clinical samples and laboratory wastes;

(h) documentation of clinical pharmacology unit observations, volunteer data and analytical data;

(i) obtaining informed consent from volunteers;

(j) volunteer screening and recruitment and management of ineligible volunteers;

(k) volunteer recycling (using the same volunteer for more than one study;

(l) randomization code management;

(m) study subject management at the site (including check-in and check-out procedures);

(n) recording and reporting protocol deviations;

(o) recording, reporting and managing scientific misconduct;

(p) monitoring and quality assurance.

(4) Wherever possible, disposable (sterile, wherever applicable) medical devices must be used for making subject interventions.

(5) If services of a laboratory or a facility other than those available at the site (whether with in India or outside the country) are to be availed – its or their names, address and specific services to be used should be documented.

2.1.5) Clinical Pharmacological Unit

(1) It must have adequate space and facilities to house at least 16 volunteers. Adequate area must be provided for dining and recreation of volunteers, separate from their sleeping area.

(2) Additional space and facilities should also be provided for the following:

(a) Office and administrative functions.

(b) Sample collection and storage.

(c) Control sample storage.

(d) Wet chemical laboratory.

(e) Instrumental Laboratory.

(f) Library.

(g) Documentation archival room.

(h) Facility for washing, cleaning and Toilets.

(i) Microbiological laboratory (Optional).

(j) Radio Immuno-Assay room (optional).

3. Maintenance of Records: All records of in *vivo* or in *vitro* tests conducted on any batch of a new drug product to assure that the product meets a bioequivalence requirement shall be maintained by the Sponsor for at least five years after the completion of any study or for at least two years after the expiration date of the batch of the new drug product whichever is later.

4. Retention of Samples: (1) All samples of test and reference drug products used in bioavailability or bioequivalence study should be retained by the organisation carrying out the bioavailability or bioequivalence study for a period of five years after the conduct of the study or one year after the expiry of the drug, whichever is later.

(2) The study sponsor or drug manufacturer should provide to the testing facility batches of the test and reference drug products in such a manner that the reserve samples can be selected randomly.

(3) This is to ensure that the samples are in fact representative of the batches provided by the study sponsor or drug manufacturer and that they are retained in their original containers. Each reserve sample should consist of a quantity sufficient to carry out twice all the in-vitro and in- vivo tests required during bioavailability or bioequivalence study.

(4) The reserve sample should be stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorised personnel.

TABLE 1

DOCUMENT REQUIRED FOR REGISTRATION OF BIOAVAILABILITY AND BIOEQUIVALENCE CENTRE

(1) Name and address of the organization to be registered along with its telephone no., fax no. and email address.

(2) Document regarding legal identity of the centre

(3) Name and address of the proprietors or partners or directors.

(4) An organogram of the centre including brief Curriculum Vitae of Key personnel (Refer para 2.1.3 of this Schedule)

(5) Documents to ensure Impartiality, confidentiality, independence and integrity of the centre**.** Refer para 2.1.2 of this Schedule.

(6) List of equipment in the firm.

(7) List of staff in firm.

(8) List of Standard Operating Procedures for various activities (refer 2.1.4 of this Schedule).

(9) Layout of facility.

(10) Details of Ethics Committee including its registration number.

(11) Facilities for maintenance of records.

(12) Details of Retention of samples.

(13) All major tie ups for ancillary services like ambulance, hospital etc.

TABLE 2
DATA AND INFORMATION REQUIRED FOR GRANT OF PERMISSION TO CONDUCT BIOAVAILABILITY AND BIOEQUIVALENCE STUDY OF A NEW DRUG OR INVESTIGATIONAL NEW DRUG

1. Introduction: A brief description of the drug and the therapeutic class to which it belongs.

2. Chemical and pharmaceutical information, Animal pharmacological and toxicological data, Clinical trial data - As per Second Schedule.

3. Published reports of Pharmacokinetic and Pharmacodynamics studies carried out in healthy subjects or patients demonstrating safety and tolerability of the molecule.

4. Regulatory status in other countries: Countries where the drug is,-

(a) Marketed.

(b) Approved.

(c) Approved as Investigational New Drug.

(d) Withdrawn, if any, with reasons.

Restrictions on use, if any, in countries where marketed or approved

Free sale certificate or certificate of analysis, as appropriate.

5. Prescribing information of the new drug in case the drug is approved for marketing in the country or other country.

6. Undertaking by the Investigator in original duly signed on a company letterhead as per Table 4 of the Third Schedule.

7. Copy of registration certificate issued by Central Licencing Authority.

8. Sponsor's Authorisation letter duly signed by the Authorised Signatory on company letterhead.

9. The study protocols, informed consent form or patient information sheet along with audio-visual recording system as per requirements of Second Schedule

10. Copy of approval of protocol from the Ethics committee, if available. Copy of registration of the Ethics Committee under rule 8 from the Central Licencing Authority.

11. The study synopsis.

12. Undertaking letter from the sponsor stating that complete medical management in accordance with rule 40 and an undertaking letter from the sponsor stating that compensation in case of study relate injury or death shall be provided in accordance with rule 39.

13. Certificate of Analysis (COA) of representative batches (both Test and Reference formulations) to be used in the BE study along with dissolution profile in case Oral Solid dosage forms.

14. For multiple dose BE study adequate supporting safety data and Pharamcokinetics or Pharmacodynamics should be submitted covering the duration of period for which the study has to be conducted. For all injectable, the sub-acute toxicity should be submitted on the Test product of the sponsor, studied in at least two species for minimum 14 days. If regulatory guidance is available provide a copy of the same.

15. For conducting Bio-Equivalence studies with reference to Cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances and radioactive substances in Healthy Human subjects a Scientific justification with special emphasis on safety of subjects with a proper risk mitigation strategy should be submitted. If regulatory guidance is available provide a copy of the same.

16. For conducting Bio-Equivalence studies with reference to cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances and radioactive substances in Patients a scientific justification with special emphasis on Safety with a proper Risk Mitigation Strategy should be submitted.

Note 1: All items may not be applicable to all drugs. For explanation, refer text of this First Schedule, Second Schedule and Third Schedule.

TABLE 3

DATA AND INFORMATION REQUIRED FOR GRANT OF PERMISSION TO CONDUCT BIOAVAILABILITY AND BIOEQUIVALENCE STUDY OF A NEW DRUG ALREADY APPROVED IN THECOUNTRY

1. Introduction: A brief description of the drug and the therapeutic class to which it belongs.
2. Chemical and pharmaceutical information **-** As per Table 2 of Second Schedule
3. Published reports of Pharmacokinetic and Pharmacodynamics studies carried out in healthy subjects or patients demonstrating safety and tolerability of the molecule.
4. Prescribing information
5. Undertaking by the Investigator in original duly signed on a company letterhead as per Table 4 of Third Schedule.
6. Copy of registration certificate issued by Central Licencing Authority.
7. Sponsor's authorisation letter duly signed by the Authorised Signatory on company letterhead.
8. The study protocols, Informed Consent Form or Patient Information Sheet along with audio-visual recording system as per requirements of Second Schedule.
9. Copy of approval of protocol from the Ethics Committee, if available.
10. Copy of registration of the Ethics Committee under rule 8 from the Central Licencing Authority.
11. The study synopsis.
12. Undertaking letter from the sponsor stating that complete medical management in accordance with rule 40 and an undertaking letter from the sponsor stating that compensation in case of study relate injury or death shall be provided in accordance with rule 39.
13. Certificate of Analysis (COA) of representative batches (both Test and Reference formulations) to be used in the Bio-Equivalence study along with dissolution profile in case Oral Solid dosage forms.
14. For multiple dose BE study adequate supporting safety data and Pharmacokinetics or Pharmacodynamics should be submitted covering the duration of period for which the study has to be conducted.
15. For all Injectable, the sub-acute toxicity should be submitted on the Test product of the sponsor, studied in at least two species for minimum 14 days. If regulatory guidance is available provide a copy of the same.
16. For conducting Bio-Equivalence studies with reference to Cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances and radioactive substances in healthy human subjects a Scientific justification with special emphasis on Safety of subjects with a proper risk mitigation strategy should be submitted. If regulatory guidance is available provide a copy of the same.
17. For conducting Bio-Equivalence studies with reference to cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances and radioactive substances in Patients a scientific justification with special emphasis on Safety with a proper risk mitigation strategy should be submitted.

FIFTH SCHEDULE

POST MARKET ASSESSMENT

(S*ee rules 77 and 82*)

1. Post marketing assessment of new drug. - (1) When a new drug is approved for marketing, assessment of safety and efficacy of the drug are generally based on data from a limited number of patients, many studied under the controlled conditions of randomized trials. Often, high risk patients and patients with concomitant illnesses that require use of other drugs are excluded from clinical trials, and long-term treatment data are limited. Moreover, patients in trials are closely monitored for evidence of adverse events.

(2) In actual clinical practice, monitoring is less intensive, a broader range of patients are treated (age, co-morbidities, drugs, genetic abnormalities), and events too rare to occur in clinical trials may be observed. Therefore, subsequent to approval of a new drug, the drug shall be closely monitored and post marketing assessment of its benefit-risk profile shall be carried out once it is marketed.

(3) A person intending to import or manufacture any new drug for sale or distribution shall have a pharmacovigilance system in place for collecting, processing and forwarding the adverse drug reaction report to the Central Licencing Authority emerging from the use of the drug imported or manufactured or marketed by the applicant in the country.

(4) The pharmacovigilance system shall be managed by qualified and trained personnel and the officer in-charge of collection and processing of data shall be a medical officer or a pharmacist trained in collection and analysis of adverse drug reaction reports.

(5) Post marketing assessment of new drug may be carried out, in different ways as under:-

(A) Phase IV (Post marketing) trial.- Phase IV (Post marketing) trial include additional drug-drug interactions, dose-response or safety studies and trials designed to support use under the approved indications, e.g. mortality or morbidity studies etc. Such trial will be conducted under an approved protocol with defined scientific objectives, inclusion and exclusion criteria, safety efficacy assessment criteria etc. with the new drug under approved conditions for use in approved patient population.

In such trial the ethical aspects for protection of rights, safety and well-being of the trial subjects shall be followed as per the regulatory provisions including that for compensation in case of clinical trial related injury or death and good clinical practices guidelines.

In such study, the study drug may be provided to the trial subject free of cost unless otherwise there is specific concern or justification for not providing the drug free of cost, to the satisfaction of the Central Licencing Authority and the ethics committee.

(B) Post marketing surveillance study or observational or non-interventional study for active surveillance.- Such studies are conducted with a new drug under approved conditions of its use under a protocol approved by Central Licencing Authority with scientific objective. Inclusion or exclusion of subject are decided as per the recommended use as per prescribing information or approved package insert.

In such studies the study drugs are the part of treatment of patient in the wisdom of the prescriber included in the protocol. The regulatory provisions and guidelines applicable for clinical trial of a new drug are not applicable in such cases as drugs are already approved for marketing.

(C) Post marketing surveillance through periodic safety update reports.- As part of post marketing surveillance of new drug the applicant shall furnish periodic safety update reports (PSURs) in accordance with the procedures as follows;

(i) The applicant shall furnish periodic safety update reports (PSURs) in order to-

(a) report all relevant new information from appropriate sources;

(b) relate the data to patient exposure;

(c) summarise the market authorisation status in different countries and any significant variations related to safety; and

(d) indicate whether changes shall be made to product information in order to optimise the use of product.

(ii) Ordinarily all dosage forms and formulations as well as indications for new drugs should be covered in one periodic safety update reports. Within the single periodic safety update reports separate presentations of data for different dosage forms, indications or separate population need to be given.

(iii) All relevant clinical and non-clinical safety data should cover only the period of the report (interval data). The periodic safety update reports shall be submitted every six months for the first two years after

approval of the drug is granted to the applicant. For subsequent two years - the periodic safety update reports need to be submitted annually. Central Licencing Authority may extend the total duration of submission of periodic safety update reports if it is considered necessary in the interest of public health. Periodic safety update reports due for a period must be submitted within thirty calendar days of the last day of the reporting period. However, all cases involving serious unexpected adverse reactions must be reported to the licencing authority within fifteen days of initial receipt of the information by the applicant. If marketing of the new drug is delayed by the applicant after obtaining approval to market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed.

(iv) New studies specifically planned or conducted to examine a safety issue should be described in the periodic safety update reports.

(v) A PSUR should be structured as follows:

(a) Title Page: The title page of periodic safety update reports should capture the name of the drug; reporting interval; permitted indication of such drug; date of permission of the drug; date of marketing of drug; licencee name and address.

(b) Introduction: This section of periodic safety update reports should capture the reporting interval; drugs intended use, mode of action, therapeutic class, dose, route of administration, formulation and a brief description of the approved indication and population.

(c) Current worldwide marketing authorisation status: This section of periodic safety update reports should capture the brief narrative over view including details of countries where the drug is currently approved along with date of first approval, date of marketing and if product was withdrawn in any of the countries with reasons thereof.

(d) Actions taken in reporting interval for safety reasons: This section of periodic safety update reports should include a description of significant actions related to safety that have been taken during the reporting interval, related to either investigational uses or marketing experience by the licence holder, sponsor of a clinical trial, regulatory authorities, data monitoring committees, or ethics committees.

(e) Changes to reference safety information: This section of periodic safety update reports should capture any significant changes to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, adverse events, and important findings from ongoing and completed clinical trials and significant non-clinical findings.

(f) Estimated patient exposure: This section of periodic safety update reports should provide the estimates of the size and nature of the population exposed to the drug. Brief descriptions of the methods used to estimate the subject or patient exposure should be provided,-

(i) Cumulative and interval subject exposure in clinical trial.

(ii) Cumulative and interval patient exposure from Marketing Experience from India.

(iii) Cumulative and interval patient exposure from Marketing Experience from rest of the world.

(g) Presentation of individual case histories: This section of periodic safety update reports should include the individual case information available to a licence holder and provide brief case narrative, medical history indication treated with suspect drug, causality assessment. Provide following information:

(i) Reference prescribing information

(ii) Individual cases received from India

(iii) Individual cases received from rest of the world

(iv) Cumulative and interval summary tabulations of serious adverse events from clinical investigations.

(v) Cumulative and interval summary tabulations from post-marketing data sources

(h) Studies: This section of periodic safety update reports should capture the brief summary of clinically important emerging efficacy or effectiveness and safety findings obtained from the licence holder, sponsored clinical trials and published safety studies that became available during the reporting interval of the report which has potential impact on product safety information.

(i) Summaries of significant safety findings from clinical trials during the reporting period;

(ii) Findings from non-interventional Studies;

(iii) Findings from non-Clinical Studies;

(iv) Findings from literature.

(i) Other information: This section of periodic safety update reports should include the details about signals and Risk Management Plan in place by licence holder (if any).

(a) Signal and risk evaluation: In this section licence holder will provide the details of signal and risk identified during the reporting period and evaluation of signals identified during the reporting period.

(b) Risk management plan: In this section licence holder will provide the brief details of safety concern and necessary action taken by him to mitigate these safety concerns.

(j) Overall Safety Evaluation: This section of periodic safety update reports should capture the overall safety evaluation of the drug based upon its risk benefit evaluation for approved indication.

(i) Summary of safety concerns

(ii) Benefit evaluation

(iii) Benefit risk analysis evaluation

(k) Conclusion: This section of periodic safety update reports should provide the details on the safety profile of drug and necessary action taken by the licence holder in this regards.

(l) Appendix: The appendix includes the copy of marketing authorisation in India, copy of prescribing information, line listings with narrative of Individual Case Safety Reports (ICSR).

SIXTH SCHEDULE

(*See rules 21, 22, 33, 34, 45, 47, 52, 53, 60, 67, 68, 75, 76, 80, 81, 86, 91, 97 and 98*)

FEE PAYABLE FOR LICENCE, PERMISSION AND REGISTRATION CERTIFICATE

Serial Number	Rule	Subject	In rupees Indian National Rupee (INR) except where specified in dollars ($)
01	21	Application for permission to conduct clinical trial	
		(i) Phase I	3,00,000
		(ii) Phase II	2,00,000
		(iii)Phase III	2,00,000
		(iv) Phase IV	2,00,000
02	22	Reconsideration of application for permission to conduct clinical trial	50,000
03	33	Application for permission toconduct bioavailability or bioequivalence study	2,00,000
04	34	Reconsideration of application of permission to conduct bioavailability or bioequivalence study	50,000

05	45	Application for registrationof bioavailability and bioequivalence study centre	5,00,000
07	47	Reconsideration of application for Registration of bioavailability and bio-equivalence study centre	1,00,000
08	52	Application for permission to manufacture new drugs or investigational new drugs for clinical trial or bioavailability or bioequivalence study	5000 per product
09	53	Reconsideration of application to manufacture new drugs or investigational new drugs for clinical trial or bioavailability or bioequivalence study	2000 per product
10	59	Application for permission to manufacture unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or bioavailability or bioequivalence study	5000 per product
11	60	Reconsideration of permission to Manufacture unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or bioavailability or bioequivalence study	2000
12	67	Application for import of new drugs or investigational new drugs for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis	5000 per product
13	68	Reconsideration of application for Import of new drugs or investigational new drugs for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis	1000
14	75	Application for permission to import new drug (Finished Formulation) for marketing	5,00,000
15		Application for permission to import new Drug (Finished Formulation) already approved in the country for marketing	2,00,000
16		Application for permission to import new drug (Active Pharmaceutical Ingredient) for marketing	5,00,000

17		Application for permission to import new drug (Active Pharmaceutical Ingredient) already approved in the country for marketing	2,00,000
18		Application for permission to import approved new drug for new claims, new indication or new dosage form or new route of administration or new strength for marketing	3,00,000
19		Application for permission to import fixed dose combination having one or more of the ingredients as unapproved new molecules for marketing	5,00,000
20		Application for permission to import fixed Dose combination having approved ingredients for marketing	4,00,000
21		Application for permission to import fixed dose combination already approved for marketing	2,00,000
22		Application for permission to import fixed dose combination for new claims, new indication or new dosage form or new route of administration or new strength for marketing	3,00,000
23	76	Reconsideration of application for permission to import new drug for marketing	50,000

24	80	Application for permission to manufacture new drug (Finished Formulation or Active Pharmaceutical Ingredient) for sale or distribution	5,00,000
25		Application for permission to manufacture new drug (Active Pharmaceutical Ingredient) already approved in the country for sale or distribution	2,00,000
26		Application for permission to manufacture new drug (Finished Formulation) for sale or distribution	5,00,000
27		Application for permission to manufacture new drug (Finished Formulation) already approved in the country for sale or distribution	2,00,000
28		Application for permission to manufacture new drug (Active Pharmaceutical Ingredient) for sale or distribution	5,00,000

29		Application for permission to manufacture new drug (Active Pharmaceutical Ingredient) already approved in the country for sale or distribution	2,00,000
30		Application for permission to manufacture approved new drug for new claims, new indication or new dosage form or new route of administration or new strength for sale or distribution	3,00,000
31		Application for permission to manufacture fixed dose combination having one or more of the ingredients as unapproved new molecules for sale or distribution	5,00,000
32	80	Application for permission to manufacture fixed dose combination having approved ingredients for sale or distribution	3,00,000
33		Application for permission to manufacture fixed dose combination already approved for sale or distribution	2,00,000
34		Application for permission to manufacture fixed dose combination for new claims, new indication or new dosage form or new route of administration or new strength for sale or distribution	3,00,000

35	80	Application for permission to manufacture new drug (Active Pharmaceutical Ingredient) or to manufacture finished formulation	5,00,000
36		Application for permission to import or to manufacture phyto-pharmaceutical drugs	2,00,000
		Reconsideration of application for	
37	81	permission to manufacture new drug for sale or distribution	50,000
		Application for Import of unapproved new	
38	86	drug by Government hospital and medical institution	10,000
		Application for permission to manufacture unapproved new drug but under clinical	
39	91	trial, for treatment of patient of life threatening disease	5,000
40	98	Pre-submission meeting	5,00,000
41	99	Post-submission meeting	50000
42	-	Any other application which is not specified above	50000

Note 1: No fee shall be chargeable in respect of application for conduct of clinical trial for orphan drugs as defined in clause (x) of rule 2.

Note 2: In case of application received from Micro Small Medium Enterprises (MSME) firms for conduct of clinical trial, approval of new drug and pre and post submission meeting, the fee payable shall be half of the fee specified above.

SEVENTH SCHEDULE

(*See rules 39, 40, and 42*)

FORMULAE TO DETERMINE THE QUANTUM OF COMPENSATION IN THE CASES OF CLINICAL TRIAL RELATED INJURY OR DEATH

1. Formula in case of clinical trial related death:

Compensation = (B x F x R) / 99.37

Where,

B = Base amount (i.e. 8 lacs)

F = Factor depending on the age of the trial subject as per **Annexure 1** (based on Workmen Compensation Act)

R = Risk Factor depending on the seriousness and severity of the disease, presence of co-morbidity and duration of disease of the trial subject at the time of enrolment in the clinical trial between a scale of 0.5 to 4 as under:

(1) 0.5 terminally ill patient (expected survival not more than (NMT) 6 months)

(2) 1.0 Patient with high risk (expected survival between 6 to 24months)

(3) 2.0 Patient with moderate risk

(4) 3.0 Patient with mild risk

(5) 4.0 Healthy Volunteers or trial subject of no risk.

However, in case of patients whose expected mortality is 90% or more within 30 days, a fixed amount of Rs. 2 lacs should be given.

2. Formula in case of clinical trial related injury (other than death): For calculation of quantum of compensation related to injury (other than death), the compensation shall be linked to the criteria considered for calculation of compensation in cases of death of the trial subject as referred to in section of this Schedule. The quantum of compensation in case of Clinical Trial related SAE should not exceed the quantum of compensation which would have been due for payment in Case of death of the trial subject since the loss of life is the maximum injury possible.As per the definition of SAE, the following sequelae other than death are possible in a clinical trial subject, in which the trial subject shall be entitled for compensation in case the SAE is related to clinical trial.

(i) A permanent disability: In case of SAE causing permanent disability to the trial subject, the quantum of compensation in case of 100% disability shall be 90% of the compensation which would have been due for payment to the nominee (s) in case of death of the trial subject.

The quantum for less than 100% disability will be proportional to the actual percentage disability the trial subject has suffered.

Accordingly, following formula shall be applicable for determination of compensation:

Compensation = (C x D x 90) / (100 x 100)

Where:

D = Percentage disability the trial subject has suffered.

C = Quantum of Compensation which would have been due for payment to the trial subject's nominees)

in case of death of the trial subject.

(ii) Congenital anomaly or birth defect: The congenital anomaly or birth defect in a baby may occur due to participation of anyone or both the parent in clinical trial. Following situations may arise due to congenital anomaly or birth defect.

(a) Still birth;

(b) Early death due to anomaly;

(c) No death but deformity which can be fully corrected through appropriate intervention;

(d) Permanent disability (mental or physical).

The compensation in such cases would be a lump sum amount such that if that amount is kept by way of fixed deposit or alike, it shall bring a monthly interest amount which is approximately equivalent to half of minimum wage of the

unskilled worker (in Delhi). The quantum of compensation in such cases of SAE shall be half of the base amount as per formula for determining the compensation for SAE resulting into death.

In case of birth defect leading to sub-clause (c) and (d) of this clause to any child, the medical management as long as required shall be provided by the Sponsor or his representative which will be over and above the financial compensation.

(iii) Chronic life-threatening disease; and

(iv) Reversible SAE in case it is resolved.

In case of clinical trial related SAE causing life-threatening disease and reversible SAE in case it is resolved, the quantum of compensation would be linked to the number of days of hospitalisation of the trial subject. The compensation per day of hospitalization shall be equal to the wage loss. The wage loss per day shall be calculated based upon the minimum wage of the unskilled worker (in Delhi).

Since, in case of hospitalisation of any patient not only the patient loses his/her wage, there will be direct or indirect losses of various kind including inconvenience, wage loss of attendant, etc. The compensation per day of hospitalisation in such case shall be double the minimum wage.

Accordingly, following formula shall be applicable for determination of compensation:

Compensation = 2 X W X N.

Where,

W = Minimum wage per day of the unskilled worker (in Delhi)

N = Number of days of hospitalization

Annexure 1

Factor (F) for calculating the amount of compensation

Age	Factor
Not more than...	
16	228.54
17	227.49
18	226.38
19	225.22
20	224.00
21	222.71
22	221.37
23	219.95
24	218.47
25	216.91
26	215.28
27	213.57
28	211.79
29	209.92
30	207.98
31	205.95
32	203.85
33	201.66
34	199.40
35	197.06
36	194.64
37	192.14
38	189.56
39	186.90
40	184.17
41	181.37
42	178.49
43	175.54
44	172.52
45	169.44
46	166.29
47	163.07

48	159.80
49	156.47
50	153.09
51	149.67
52	146.20
53	142.68
54	139.13
55	135.56
56	131.95
57	128.33
58	124.70
59	121.05
60	117.41
61	113.77
62	110.14
63	106.52
64	102.93
65 or more	99.37

EIGHTH SCHEDULE

FORM CT-01

(*See rules 8, 10 and 17*)

APPLICATION FOR REGISTRATION/RENEWAL OF ETHICS COMMITTEE RELATING TO CLINICAL TRIAL OR BIOAVAILABILITY AND BIOEQUIVALNENCE STUDY OR BIOMEDICAL HEALTH RESEARCH

I/We, ...*(name, designation and full postal address of the applicant)* of ..... (*name and full address with contact details of the ethics committee*) hereby apply for grant of registration of ethics committee.

The details of the application are as under:

1. Name of applicant:
2. Nature and constitution of applicant: (proprietorship, company, society, trust, independent, institutional, other to be specified)
3. (i) Applicant address including telephone number, mobile number, fax number and e-mail id: (ii) Address for correspondence: corporate or registered office or clinical trial site or bioavailability and bioequivalence study centre or biomedical health research
4. Details of accreditation, if any (self-attested copy of certificate to be attached):
5. I have enclosed the documents as specified in the Table 1 of the Third Schedule of the New Drugs and Clinical Trials Rules, 2019.

6. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940, and the New Drugs and Clinical Trials Rules, 2019.

Place: _____ Digital Signature

Date: _____ (Name and designation)

FORM CT-02

(*See rules 8, 9, 10 and 14)*

GRANT OF REGISTRATION OF ETHICS COMMITTEE RELATING TO CLINICAL TRIAL OR BIOAVAILABILITY AND BIOEQUIVALNENCE STUDY

Registration No._____

The Central Licencing Authority here by registers and permits___(Name and full address with contact details of the ethics committee) to perform duties of ethics committee as specified in the New Drugs and Clinical Trials Rules, 2019.

2. The ethics committee shall observe the conditions of registration specified in Chapter III of the New Drugs and Clinical Trials Rules, 2019 and the Drugs and Cosmetics Act, 1940.

Place: …… Central Licencing Authority

Date: ..... Stamp

FORM CT-03

(*See rules 17 and 18)*

GRANT OF REGISTRATION OF ETHICS COMMITTEE RELATING TO BIOMEDICAL HEALTH RESEARCH

Registration No._____

The designated authority is hereby register and permit_____
(Name and full address with contact details of the ethics committee) to perform duties of ethics committee as specified in the Regulation of New Drugs and Clinical Trials Rules, 2019.

2. The ethics committee shall observe the conditions of registration specified in Chapter IV of the New Drugs and Clinical Trials Rules, 2019 and the Drugs and Cosmetics Act, 1940.

Place: …… Central Licencing Authority

Date: ..... Stamp

FORM CT-04

(*See rule 21*)

APPLICATION FOR GRANT OF PERMISSION TO CONDUCT CLINICAL TRIAL OF NEW DRUG OR INVESTIGATIONAL NEW DRUG

I/We, ...*(name and full postal address of the applicant)* of ..... hereby apply for grant of permission to conduct clinical trial on new drug or investigational new drug.

The details of the application are as under:

1.Name of Applicant:	
2. Nature and constitution: proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified.	
3. (i) Sponsor address, telephone number, mobile number, fax number and e-mail id: (ii) Clinical trials site address, telephone number, mobile number, fax number and e-mail id: (iii) Name and address of person responsible for payment of compensation, if any: (iv) Address for correspondence: [corporate or registered office or clinical trial site]	
4. Details of new drugs or investigational new drugs and clinical investigation site [As per Annexure].	
5. Phase of the Clinical Trial	
6. Clinical trial protocol number with date:	
7. Fee paid on _____ Rs. _____ Receipt or Challan or transaction ID_____.	
8. I have enclosed the documents as specified in the Second Schedule of the New Drugs and Clinical Trials Rules, 2019.	
9. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940, and the New Drugs and Clinical Trials Rules, 2019.	

Place:……. Digital Signature

Date:……..... (Name and designation)

Annexure:

Details of new drugs or investigational new drugs:

Names of the new drug or investigational new drug:	
Therapeutic class:	
Dosage form:	

Composition:	
Indications:	

Details of clinical trial site:

Names and address of clinical trial site	
Ethics committee details:	
Name of investigator:	

FORM CT-4A

(*See rule 23*)

INFORMATION TO INITIATE CLINICAL TRIAL OF NEW DRUG OR INVESTIGATIONAL NEW DRUG AS PART OF DISCOVERY, RESEARCH AND MANUFACTURE IN INDIA

I/We, ...*(name and full postal address of the applicant)* of ..... hereby inform to initiate the conduct clinical trial on new drug or investigational new drug.

The details of the application areas under:

1.Name of Applicant:	
2. Nature and constitution: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3. (i) Sponsor address, telephone number, mobile number, fax number and e-mail id: (ii) Clinical trials site address, telephone number, mobile number, fax number and e-mail id: (iii) Name and address of person responsible for payment of compensation, if any: (iv) Address for correspondence: [corporate or registered office or clinical trial site]	
4. Details of new drugs or investigational new drugs and clinical investigation site [As per Annexure].	
5. Phase of the Clinical Trial	
6. Clinical trial protocol number with date:	
8. I hereby declared that I have already submitted the application under rule 21 of these rules and granted automatic approval under rule 23(2) and enclosed the documents as specified in the Second Schedule of the New Drugs and Clinical Trials rules, 2019.	
9. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940, and the New Drugs and Clinical Trials Rules, 2019.	

Place:…….

Date:…….....

Digital Signature

(Name and designation)

Annexure:

Details of new drugs or investigational new drugs:

Names of the new drug or investigational new drug:	
Therapeutic class:	
Dosage form:	
Composition:	
Indications:	

Details of clinical trial site:

Names and address of clinical trial site	
Ethics committee details:	
Name of investigator:	

FORM CT-05

(See rule 33)

APPLICATION FOR GRANT OF PERMISSION TO CONDUCT BIOAVAILABILITY OR BIOEQUIVALENCE STUDY

I/We, ...*(name and full postal address of the applicant)* of ..... hereby apply for grant of permission to conduct bioavailability or bioequivalence study (*strike off whichever is not applicable*) of new drug or investigational new drug, the details of which are as under:

1.Name of applicant:	
2. Nature and constitution: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3. (i) Sponsor address, telephone number, mobile number, fax number and e-mail id: (ii) Study address, telephone number, mobile number, fax number and e-mail id: (iii) Address for correspondence: [corporate or registered office or bioavailability or bioequivalence study centre]	

4. Details of new drug or investigational new drug and study centre [As per Annexure].
5. Study protocol number with date:
6. Fee paid on _____ Rs. _____ Receipt or challan or transaction ID_____.
7. I have enclosed the documents as specified in the Fourth Schedule of the New Drugs and Clinical Trials Rules, 2019.
8. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940, and the New Drugs and Clinical Trials Rules, 2019.

Place:……. Digital Signature

Date:……..... (Name and designation)

Annexure:

Details of new drug or investigational new drugs:

Names of the new drug or investigational new drug:	
Therapeutic class:	
Dosage form:	
Composition:	
Indications:	

Details of study centre:

Names and address of study centre	
Ethics committee details:	

FORM CT-06

(See rules 22, 25, 26, 29 and 30)

PERMISSION TO CONDUCT CLINICAL TRIAL OF NEW DRUG OR INVESTIGATIONAL NEW DRUG

The Central Licencing Authority hereby permits_____

(Name and full address with contact details of the applicant) to conduct clinical trial of the new drug or investigational new drug as per protocol number _____in the below mentioned clinical trial sites. dated

2. Details of new drug or investigational new drug and clinical trial site [As per Annexure].

3. This permission is subject to the conditions prescribed in part A of Chapter V of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act, 1940.

Place: ……. Central Licencing Authority

Date: ..... Stamp

Annexure:

Details of new drug or investigational new drug:

Names of the new drug or investigational new drug:	
Therapeutic class:	
Dosage form:	
Composition:	
Indications:	

Details of clinical trial site:

Names and address of clinical trial site	
Ethics committee details:	
Name of principal investigator:	

FORM CT-07

(See Rules 34, 35, 36, 37 and 38)

PERMISSION TO CONDUCT BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OF NEW DRUG OR INVESTIGATIONAL NEW DRUG

The Central Licencing Authority hereby permits_____
(Name and full address with contact details of the applicant) to conduct bioavailability or bioequivalence study (*strike off whichever is not applicable*) of the new drug or investigational new drug as per protocol number_____dated___in the below mentioned study centre.

2. Details of new drug or investigational new drug and study centre [As per Annexure].

3. This permission is subject to the conditions prescribed in part B of Chapter V of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act, 1940.

Place: …… Central Licencing Authority

Date: ..... Stamp

Annexure:

Details of new drug or investigational new drug:

Names of the new drug or investigational new drug:	
Therapeutic class:	
Dosage form:	
Composition:	
Indications:	

Details of study centre:

Names and address of study centre:	
Ethics committee details:	
Name of principal investigator:	

FORM CT-08

(*See rule45*)

APPLICATION FOR REGISTRATION/RENEWAL OF BIOAVAILABILITY OR BIOEQUIVALENCE STUDY CENTRE

I/We, ...*(name, designation and full postal address of the applicant)* of ..... hereby apply for grant of registration of bioavailability or bioequivalence study centre. The details of the application are as under:

1.Name of applicant:	
2. Nature and constitution of applicant: (proprietorship, company, society, trust, independent, institutional, other to be specified)	
3. (i) Applicant address including telephone number, mobile number, fax number and e-mail id: (ii) Address for correspondence: [corporate or registered office or bioavailability or bioequivalence study centre]	
4. Details of accreditation, if any (self-attested copy of certificate to be attached):	
5. Fee paid on _____ Rs. _____ Receipt or challan or transaction ID_____.	
6. I have enclosed the documents as specified in the Table 1 of Fourth Schedule of the New Drugs and Clinical Trials Rules, 2019.	
7. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940 the New Drugs and Clinical Trials Rules, 2019.	

Place: ……..

Date: ……

Digital Signature

(Name and designation)

FORM CT-09

(*See rules 47, 48, 49, 50and 51*)

GRANT OF REGISTRATION OF BIOAVAILABILITY OR BIOEQUIVALENCE STUDY CENTRE

Registration No._____

The Central Licencing Authority hereby register_____
(Name and full address with contact details of the applicant) for conduct of bioavailability and bioequivalence studies of new drugs and investigational new drugs as specified in the New Drugs and Clinical Trials Rules, 2019.

2.This registration is subject to the conditions prescribed in Chapter VII of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act, 1940.

Place: …….

Date: .....

Central Licencing Authority

Stamp

FORM CT-10

(*See rule 52)*

APPLICATION FOR GRANT OF PERMISSION

TO MANUFACTURE NEW DRUG OR INVESTIGATIONAL NEW DRUG FOR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

I/We, ...

(name and full postal address of the applicant) of ..... hereby apply for grant of permission to manufacture new drug or investigational new drug for clinical trial or bioavailability or bioequivalence study or for examination, test and analysis.

The details of the application are as under:

1. Name of applicant:	
2. Nature and constitution of applicant: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3.(i) Corporate or Registered office address, telephone number, mobile number, fax number and e-mail id: (ii) Applicant's address, telephone number, mobile number, fax number and e-mail id: (iii) Address for correspondence:	
4. Details of new drugs and investigational new drugs to be manufactured [As per Annexure].	
5. Particulars of Manufacturer, Manufacturing sites [As per Annexure].	
6. Fee paid on _____Rs_____receipt or challan or transaction ID___.	

7. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940 and the Chapter VIII of New Drugs and Clinical Trials Rules, 2019. (ii) The new drug to be manufactured from M/s..... shall be used exclusively for the purpose of clinical trial and no part of it shall be diverted to the domestic market.

Place: …… Date:	Digital Signature (Name and designation)

Annexure:

Details of new drug or investigational new drug:

Names of the new drug or investigational new drug:	
Therapeutic class:	
Dosage form:	
Composition:	
Indications:	

Details of manufacturer and manufacturing site:

Name and address of Active Pharmaceutical Ingredient and formulation manufacturer (full address with telephone, fax and e-mail address of the manufacturer).	
Name and address of manufacturing sites of Active Pharmaceutical Ingredient and formulation (full address with telephone, fax and e-mail address of the manufacturing site).	

FORM CT-11

(*See rules 53, 54, 55, 56, 57 and 58)*

PERMISSION TO MANUFACTURE NEW DRUG OR INVESTIGATIONAL NEW DRUG FOR CLINICAL TRIAL, BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

Licence Number _____

The Central Licencing Authority hereby grant permission _____ (Name and full postal address with contact details of the applicant) to manufacture the new drug or investigational new drug for conduct of clinical trial or bioavailability or bioequivalence study as per protocol number_____dated_____in the below mentioned clinical trial sites or bioavailability and bioequivalence study centre [As per Annexure] or for examination, test and analysis.

Serial Number	Name of the new drug or investigational new drug to be manufactured.	Class of new drug or investigational new drug.	Quantity to be manufactured.

2. This licence is subject to the conditions specified in the Chapter VIII of New Drugs and Clinical Trials Rules,2019 under the Drugs and Cosmetics Act, 1940.

3. This licence shall, unless previously suspended or revoked, be in force for a period of three years from the date of its issuance.

4. Details of manufacturer and manufacturing site under this licence.

Serial Number	Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer).	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site).

Place: …….

Date: .....

Central Licencing Authority

Stamp

Annexure:

Details of clinical trial site:

Names and address of clinical trial site	
Ethics committee details:	
Name of investigator:	

FORM CT-12

(*See rule 59)*

APPLICATION FOR GRANT OF PERMISSION TO MANUFACTURE FORMULATION OF UNAPPROVED ACTIVE PHARMACEUTICAL INGREDIENT FOR TEST OR ANALYSIS OR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY

I/We, ...*(name and full postal address of the applicant)* of ..... hereby apply for grant of permission to manufacture formulations of unapproved active pharmaceutical ingredient for test or analysis or clinical trial or bioavailability or bioequivalence study.

The details of the application are as under:

1. Name of formulation manufacturer:	
2. Nature and constitution of applicant: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3.(i) Corporate or registered office address telephone number, mobile number, fax number and e-mail id: (ii) Formulation manufacturer's address including telephone number, mobile number, fax number and e-mail id: (iii) Address for correspondence:	

4. Details of unapproved Active pharmaceutical ingredient and its formulation [As per Annexure].
5. Details of Manufacturer, Manufacturing sites of formulation [As per Annexure].
6.Fee paid on _____ Rs__ receipt or challan or transaction ID.
7. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940 and Chapter VIII of the New Drugs and Clinical Trials Rules, 2019. (ii) The formulation of the unapproved active pharmaceutical ingredient to be manufactured shall be used for the mentioned purpose only and no part of it shall be sold in the market.

Place: Digital Signature

Date: (Name and designation)

Annexure:

Details of Active pharmaceutical ingredient and its formulation:

Name of the unapproved active pharmaceutical ingredient (API)	Quantity	Name of the formulation/test Batches to be developed for test/analysis or clinical trial	Quantity

Name of the formulation to be manufactured	
Quantity	
Composition	
Indication	

Details of manufacturer and manufacturing site of formulation:

Serial number	Name and address of manufacturer of formulation (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of manufacturing site of formulation (full address with telephone, fax and e-mail address of the manufacturing site)

Details of manufacturer and manufacturing site of Active pharmaceutical ingredient:

Serial number	Name and address of manufacturer of Active pharmaceutical ingredient (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of manufacturing site of Active pharmaceutical ingredient (full address with telephone, fax and e-mail address of the manufacturing site)

FORM CT-13

(*See rule 59 and 60)*

APPLICATION FOR GRANT OF PERMISSION TO MANUFACTURE UNAPPROVED ACTIVE PHARMACEUTICAL INGREDIENT FOR DEVELOPMENT OF FORMULATION FOR TEST OR ANALYSIS OR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY

I/We, ...*(name and full postal address of the applicant)* of ..... hereby apply for grant of permission to manufacture unapproved active pharmaceutical ingredient for development of formulation for test or analysis or clinical trial or bioavailability or bioequivalence study.

The details of the application are as under:

1. Name of manufacture:	
2. Nature and constitution of applicant: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3.(i) Corporate or registered office address telephone number, mobile number, fax number and e-mail id: (ii) Formulation manufacturer's address including telephone number, mobile number, fax number and e-mail id: (iii) Address for correspondence:	
4. Details of unapproved active pharmaceutical ingredient to be manufactured [As per Annexure].	
5. Details of formulation to be manufactured [As per Annexure].	
6. Fee paid on_____Rs_____ receipt or challan or transaction ID_____.	
(i) I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940 and Chapter VIII of the New Drugs and Clinical Trials Rules, 2019. (ii) The unapproved active pharmaceutical ingredient to be manufactured shall be supplied to M/s ……only and no part of it shall be sold in the market.	

Place: Digital Signature

Date: (Name and designation)

Annexure:

Details of Active pharmaceutical ingredient and its formulation:

Name of the unapproved active pharmaceutical ingredient (API) to be obtained	Quantity	Name of the formulation or test batches to be developed for test/analysis or clinical trial	Quantity

Details of manufacturer and manufacturing site of formulation:

Serial number	Name and address of manufacturer of formulation (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of manufacturing site of formulation (full address with telephone, fax and e-mail address of the manufacturing site)

Details of manufacturer and manufacturing site of Active pharmaceutical ingredient:

Serial number	Name and address of manufacturer of Active pharmaceutical ingredient (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of manufacturing site of Active pharmaceutical ingredient (full address with telephone, fax and e-mail address of the manufacturing site)

FORM CT-14

(*See rules 60, 61, 62, 63and64*)

PERMISSION TO MANUFACTURE FORMULATION OF UNAPPROVED ACTIVE PHARMACEUTICAL INGREDIENT FOR TEST OR ANALYSIS OR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY

Licence Number:_____

The Central Licencing Authority hereby grant permission to _____
(Name and full postal address with contact details of the formulation manufacturer) to manufacture the formulation of the unapproved active pharmaceutical ingredient specified below for test or analysis or for conduct of clinical trials bioavailability or bioequivalence study.

Name of the formulation or test batches to be developed for test or analysis or clinical trial	Quantity

2. Details of manufacturer, manufacturing site of formulation [As per Annexure].

Serial number	Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site)

3. This licence is subject to the conditions prescribed under Chapter VII of the New Drugs and Clinical Trials Rules,2019 under the Drugs and Cosmetics Act,1940.

4. Details of manufacturer and manufacturing site of active pharmaceutical ingredient to be supplied.

Serial number	Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site)

5. This licence shall, unless previously suspended or revoked, be in force fora period of ..... from the date of its issuance.

Place:…….

Date: .....

Central Licencing Authority

Stamp

FORM CT-15

(*See rules 60, 61, 62, 63 and 64*)

PERMISSION TO MANUFACTURE UNAPPROVED ACTIVE PHARMACEUTICAL INGREDIENT FOR THE DEVELOPEMNT OF FORMULATION FOR TEST OR ANALYSIS OR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY

Licence Number:_____

The Central Licencing Authority hereby grant permission to_____
(Name and full address of the active ingredient manufacturer) to manufacture the unapproved active pharmaceutical ingredient specified below to manufacture its formulation for test or analysis or for conduct of clinical trials or bioavailability or bioequivalence study.

Name of the unapproved active pharmaceutical ingredient (API) to be manufactured	Quantity

2. Details of Manufacturer, Manufacturing site of active pharmaceutical ingredient.

Serial number	Name and address of manufacturer (full address with telephone, fax and e- mail address of the manufacturer)	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site)

3. Details of Manufacturer, Manufacturing site of formulation manufacturer to be supplied.

Serial. number	Name and address of formulator (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of site where the manufactured unapproved active pharmaceutical ingredient to be used (full address with telephone, fax and e-mail address of the manufacturing site)

4. This permission is subject to the conditions specified in Chapter VIII of the New Drugs and Clinical Trials Rules,2019 under the Drugs and Cosmetics Act, 1940.

5. This permission shall, unless previously suspended or revoked, be in force for a period of ..... from the date of its issuance.

Place:……. Central Licencing Authority

Date: ..... Stamp

Annexure

Details of record of unapproved active pharmaceutical ingredient manufactured:

Serial number	Date of manufacture	Licence number	Name of the unapproved active pharmaceutical ingredient	Quantity manufactured	Manufactured for

Details of reconciliation of unapproved active pharmaceutical ingredient manufactured:

Date	Name of the unapproved active pharmaceutical ingredient	Licence number	Quantity manufactured	Quantity supplied	Quantity remained	Supplied to	Quantity – left over or remain unused or got damaged or expired or found of sub-standard quality	Action taken

*** Write NA where not applicable.**

FORM CT-16

(*See rule 67*)

APPLICATION FOR GRANT OF LICENCE TO IMPORT NEW DRUG OR INVESTIGATIONAL NEW DRUG FOR CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

I/We, ...*(name and address of the applicant)* of M/s ..... hereby apply for grant of licence to import new drug or investigational new drug for clinical trial bioavailability or bioequivalence study or for examination, test and analysis.

The details of the application are as under:

1. Name of applicant:	
2. Nature and constitution of applicant: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	

3.(i) Corporate or registered office address including telephone number, mobile number, fax number and e-mail id: (ii) Applicant's address including telephone number, mobile number, fax number and e- mail id: (iii) Address for correspondence:	
4. Details of new drugs to be imported [As per Annexure].	
5. Particulars of overseas Manufacturer, Manufacturing sites [As per Annexure].	
6. Fee paid on _____ Rs_____ receipt or challan or transaction ID.	
7. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940 and Chapter IX of the New Drugs and Clinical Trials Rules, 2019. (ii) The new drug to be imported from M/s..... shall be used exclusively for the purpose of clinical trial and no part of it shall be diverted to the domestic market.	

Place: Digital Signature

Date: (Name and designation)

Annexure:

Details of new drug or investigational new drug:

Names of the new drug or investigational new drug:	
Therapeutic class:	
Dosage form:	
Composition:	
Indications:	

Details of manufacturer and manufacturing site:

Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer)	
Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site)	

FORM CT-17

(*See rules 68, 69, 70, 71 and 72*)

LICENCE TO IMPORT NEW DRUG OR INVESTIGATIONAL NEW DRUG FOR THE PURPOSE OF CLINICAL TRIAL OR BIOAVAILABILITY OR BIOEQUIVALENCE STUDY OR FOR EXAMINATION, TEST AND ANALYSIS

Licence Number:_____

The Central Licencing Authority hereby grants licence to _____(Name and full address with contact details of the applicant) to import new drug or investigational new drug for conduct of clinical trial or bioavailability or bioequivalence study as per protocol number dated

_____or for examination, test and analysis in the below mentioned clinical trial sites or bioavailability or bioequivalence study centre. [As per Annexure].

Serial number	Name of the new drug or investigational new drug to be imported	Therapeutic class of new drug or investigational new drug	Quantity to be imported

2. This licence is subject to the conditions prescribed in Chapter IX of the New Drugs and Clinical Trials Rules, 2019.

3. This licence shall, unless previously suspended or revoked, be in force for a period of three years from the date of its issuance.

4. Details of overseas manufacturer and manufacturing site under this licence.

Serial number	Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer)	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site)

5. The licencee shall maintain the record of imported new drug or investigational new drugs [As per Annexure].

Place: ……. Central Licencing Authority

Date: ..... Stamp

Annexure:

Details of clinical trial site or bioavailability or bioequivalence study centre:

Names and address:	
Ethics committee details:	
Name of investigator:	

FORM CT-18

(*See rule 75*)

APPLICATION FOR GRANT OF PERMISSION TO IMPORT NEW DRUG FOR SALE OR FOR DISTRIBUTION

I/We, ... *(name and address of the applicant)* of M/s ..... hereby apply for grant of permission to import new drug for sale.

1. Name of applicant:	
2. Nature and constitution of applicant: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3.(i) Corporate or registered office address including telephone number, mobile number, fax number and e-mail id: (ii) Manufacturer's address including telephone number, mobile number, fax number and e-mail id: (iii) Address for correspondence:	
4. Details of new drug to be imported (Active pharmaceutical Ingredient or Finished Formulation) [As per Annexure].	
5. Details of the manufacturer and manufacturing site [As per Annexure].	
6. Fee paid on _____ Rs_____ receipt or challan or transaction ID_____.	
7. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940 and Chapter X of the New Drugs and Clinical Trials Rules, 2019.	

Place: Digital Signature

Date: (Name and designation)

Annexure:

Details of new drug:

Name of the new drug:	
Dosage form:	
Composition of the formulation:	
Therapeutic class of the new drug:	
Indications for which proposed to be used:	
Manufacturer of the raw material (active pharmaceutical ingredient):	

Details of manufacturer and manufacturing site of new drug:

Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer).	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site).

FORM CT-19

(*See rules 76, 77 and 78*)

PERMISSION TO IMPORT NEW ACTIVE PHARMCEUTICAL INGREDIENT FOR SALE OR FOR DISTRIBUTION

The Central Licencing Authority hereby grants permission to_____
(Name and full postal address of authorised agent with contact details of the organization) to import new active pharmaceutical ingredient manufactured by an overseas manufacturer specified below for sale.

2. Details of overseas manufacturer and its manufacturing site under this licence.

Serial number	Name and address of overseas manufacturer (full name and address with telephone and e-mail address of manufacturer)	Name and address of manufacturing site (full name and address with telephone and e-mail address of manufacturing site)

3. This permission is subject to the conditions prescribed in Chapter X of the New Drugs and Clinical Trials Rules,2019 under the Drugs and Cosmetics Act,1940.

4. Details of active pharmaceutical ingredient to be imported.

Name of the active pharmaceutical ingredient to be obtained.	Quantity.

Place: …….
Date: .....

Central Licencing Authority
Stamp

FORM CT-20

(*See rules 76, 77 and 78*)

PERMISSION TO IMPORT PHARMACEUTICAL FORMULATIONS OF NEW DRUG FOR SALE OR FOR DISTRIBUTION

The Central Licencing Authority hereby grant permission to_____
(Name and full postal address of authorised agent with contact details of the organisation) to import pharmaceutical formulation manufactured by an overseas manufacturer specified below for sale.

2. Details of overseas manufacturer and its manufacturing site under this licence.

Serial number	Name and address of overseas manufacturer (full name and address with telephone and e-mail address of manufacturer).	Name and address of manufacturing site (full name and address with telephone and e-mail address of manufacturing site)

3. Details of pharmaceutical formulation:

Name of the new drug to be imported:	
Dosage form:	
Composition:	
Indication:	

4. This permission is subject to the conditions prescribed in Chapter X of the New Drugs and Clinical Trials Rules,2019 under the Drugs and Cosmetics Act,1940.

Place: ……. Central Licencing Authority

Date: ..... Stamp

FORM CT-21

(*See rule 80)*

APPLICATION FOR GRANT OF PERMISSION TO MANUFACTURE NEW DRUG FORMULATION FOR SALE OR FOR DISTRIBUTION

I/We, ... *(name and full postal address of the applicant)* of M/s ..... hereby apply for grant of permission to manufacture new drug for sale or distribution.

The details of the application are as under:

1. Name of applicant:	
2. Nature and constitution of applicant: (i.e. proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3.(i) Corporate or registered office address including telephone number, mobile number, fax number and e-mail id: (ii) Manufacturer's address including telephone number, mobile number, fax number and e-mail id: (iii) Address for correspondence:	
4. Details of new drug to be manufactured (Active pharmaceutical Ingredient or Finished Formulation or both) [As per Annexure].	
5. Details of the manufacturer and manufacturing site [As per Annexure].	
6. Fee paid on _____Rs__ receipt or challan or transaction ID.	

7. I hereby state and undertake that: (i) I shall comply with all the provisions of the Drugs and Cosmetics Act, 1940 and Chapter X of the New Drugs and Clinical Trials Rules, 2019.

Place:…….. Digital Signature

Date: …… (Name and designation)

Annexure:

Details of new drug:

Name of the new drug:	
Dosage form:	
Composition of the formulation:	
Therapeutic class of the new drug:	
Indications for which proposed to be used:	

Details of manufacturer and manufacturing site of new drug:

Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer).	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site).

FORM CT-22

(*See rules 81, 82, 83 and 84*)

PERMISSION TO MANUFACTURE NEW ACTIVE PHARMACEUTICAL INGREDIENT FOR SALE OR FOR DISTRIBUTION

The Central Licencing Authority hereby grant permission to …… (Name and full address with contact details of the manufacturer) to manufacture for sale the new active pharmaceutical ingredient manufactured by manufacturer specified below.

2. Details of manufacturer and its manufacturing site under this permission.

Serial number	Name and address of manufacturer (full name and address with telephone and e-mail address of manufacturer)	Name and address of manufacturing site (full name and address with telephone and e-mail address of manufacturing site)

3. This is subject to the conditions specified in Chapter X of the New Drugs and Clinical Trials Rules,2019 under the Drugs and Cosmetics Act,1940.

4. Details of the new active pharmaceutical ingredient to be manufactured------.

Place: ……. Central Licencing Authority

Date: ..... Stamp

FORM CT-23

(*See rules 81, 82, 83 and 84*)

PERMISSION TO MANUFACTURE PHARMACEUTICAL FORMULATION OF NEW DRUG FOR SALE OR FOR DISTRIBUTION

The Central Licencing Authority hereby grant permission to …… (Name and full address of authorised agent with contact details of the manufacturer) to manufacture for sale of pharmaceutical formulation manufactured by an manufacturer specified below.

2. Details of manufacturer and its manufacturing site under this licence.

Serial number	Name and address of manufacturer (full name and address with telephone and e-mail address of manufacturer).	Name and address of manufacturing site (full name and address with telephone and e-mail address of manufacturing site).

3. Details of pharmaceutical formulation:

Name of the new drug to be imported:	
Dosage form:	
Composition:	
Indication:	
Shelf life with storage condition:	

4. This is subject to the conditions prescribed in Chapter X of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act,1940.

Place: ……. Central Licencing Authority

Date: ..... Stamp

FORM CT-24

(See rule 86)

APPLICATION FOR LICENCE TO IMPORT OF UNAPPROVED NEW DRUG FOR TREATMENT OF PATIENTS OF LIFE THREATENING DISEASE IN A GOVERNMENT HOSPITAL OR GOVERNMENT MEDICAL INSTITUTION

I/We, ...

(name and full postal address of the applicant) of M/s ..... hereby apply for grant of licence to import unapproved new drug but under clinical trial for treatment of patients of life threatening disease in a government hospital or medical institution.

The details of the application are as under:

1. Name of Medical officer:	
2. Nature and constitution of applicant: (Government Hospital or Medical Institution)	
3.(i) Aaddress including telephone number, mobile number, fax number and e-mail id of the Government Hospital or Medical Institution: (ii) Address for correspondence:	
4. Details of unapproved new drug pharmaceutical formulation to be imported [As per Annexure].	
5. Details of the manufacturer and manufacturing site [As per Annexure].	
6. Details of the patient and disease [As per Annexure].	
7. Fee paid on _____ Rs__ receipt or challan or transaction ID.	
8. A legal undertaking stating that the unapproved new drug to be imported shall be used for the treatment of the patient for the disease mentioned below only and no part of it shall be sold in the market is enclosed herewith.	

Place: …… Digital Signature

Date: ……. (Name and designation)

Annexure:

Details of unapproved new drug to be imported:

Name of the new drug:	
Dosage form:	
Quantity:	
Indications for which proposed to be used:	

Details of manufacturer and manufacturing site:

Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer).	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site).

Details of patient:

Name of the patient:	
Disease name:	

Certificate

Certified that the unapproved new drug specified above for import is urgently required for the treatment of patients suffering from…….. and that the said drug is not available in India.

Place..... Signature

Date..... Medical Superintendent of the Government Hospital or Head of Medical Institution

[Stamp]

FORM CT-25

(See rules 87, 88, 89 and 90)

LICENCE TO IMPORT UNAPPROVED NEW DRUG FOR TREATMENT OF PATIENTS OF LIFE THREATENING DISEASE IN A GOVERNMENT HOSPITAL OR MEDICAL INSTITUTION

Licence Number:_____

The Central Licencing Authority hereby grant license to_____(Name and full postal address with contact details of the Government Hospital or Government Medical Institution) to import the unapproved new drug specified below for the purpose of treatment of the patient for the disease …… (Name of the disease).

2. This permission is subject to the conditions prescribed in Chapter XI of the New Drugs and Clinical trials Rules,2019 under the Drugs and Cosmetics Act, 1940.

3. This licence shall, unless previously suspended or revoked, be in force for a period of ..... from the date of its issuance.

4. Details of the new drug to be imported

Name of new drug:	
Quantity to be imported:	

Place: ……. Central Licencing Authority

Date: ..... Stamp

Annexure

Details of new drug imported:

Serial number	Date of import.	Licence number	Name of the new drug imported.	Imported through (Port office name).	Consignment number	Quantity imported.

Details of record of patient history:

Licence number	Name of the new drug.	Patient name	Diagnosis detail with date.	Disease name.	Dosage schedule.

Details of reconciliation of new drug to be imported:

Date	Nam e of the new drug.	Licence number.	Initial quantity.	Quantity used.	Quantity remained.	Quantity – left over or remain unused or got damaged or expired or found of sub-standard quality	Action taken.

*Write NA where not applicable.

FORM CT-26

(See rule 91)

APPLICATION FOR GRANT OF PERMISSION TO MANUFACTURE UNAPPROVED NEW DRUG BUT UNDER CLINICAL TRIAL FOR TREATMENT OF PATIENTS OF LIFE THREATENING DISEASE IN A GOVERNMENT HOSPITAL OR MEDICAL INSTITUTION

I/We, ... *(name and full postal address of the applicant)* of M/s ..... hereby apply for grant of permission to manufacture unapproved new drug but under clinical trial for treatment of patients of life threatening disease in a government hospital or medical institution.

The details of the application are as under:

1. Name of applicant:	
2. Nature and constitution of applicant: (proprietorship, partnership including limited liability partnership, company, society, trust, other to be specified)	
3.(i) Corporate or registered office address including telephone number, mobile number, fax number and e-mail id: (ii) Manufacturer's address including telephone number, mobile number, fax number and e-mail id: (iii) Address for correspondence:	
4. Details of unapproved new drug to be manufactured [As per Annexure].	
5. Details of the manufacturer and manufacturing site [As per Annexure].	
6. Details of the Medical officer and Government Hospital and Medical Institution	
7. Copy of recommendation of the ethics committee and consent from the patient in accordance with Rule 81 of the Regulation of New Drugs and Clinical Trials Rules 2019 are hereby enclosed.	

8. Fee paid on _____Rs_____ receipt or challan or transaction ID___.
9. A legal undertaking stating that the unapproved new drug to be manufactured shall be used for the treatment of the patient for the disease mentioned below only and no part of it shall be sold in the market is enclosed herewith.

Place:……. Digital Signature

Date: ……. (Name and designation)

Annexure:

Details of unapproved new drug to be manufactured:

Name of the new drug:	
Quantity:	
Indications:	

Details of manufacturer and manufacturing site:

Name and address of manufacturer (full address with telephone, fax and e-mail address of the manufacturer).	Name and address of manufacturing site (full address with telephone, fax and e-mail address of the manufacturing site).

Details of the government hospital or government medical institution and patient:

Name of the government hospital or government medical institution:	
Address of the government hospital or government medical institution:	
Name and address of the patient:	
Disease name:	

Certificate

Certified that the unapproved new drug but under clinical trial specified above for manufacture is urgently required for the treatment of patients suffering from_____and that the said drug(s) is/are not available in India.

Place..... Signature

Date..... Medical Superintendent of the Government Hospital or Head of Medical Institution

[Stamp]

FORM CT-27

(See rules 92, 93, 94 and 95)

PERMISSION TO MANUFACTURE UNAPPROVED NEW DRUG BUT UNDER CLINICAL TRIAL FOR TREATMENT OF PATIENTS OF LIFE THREATENING DISEASE IN A GOVERNMENT HOSPITAL OR MEDICAL INSTITUTION

Licence Number ……

The Central Licencing Authority hereby grant permission to ……. (Name and full postal address with contact details of the organization) to manufacture the unapproved new drug specified below on the premises situated at ……..……..... (full postal address with contact details of the manufacturing site) for supply to …… (name of the medical officer and address of the Government hospital or medical institution) for the treatment of the patient for the disease …… (Name of the disease).

2. This licence is subject to the conditions prescribed in Chapter XI of the New Drugs and Clinical Trials Rules, 2019 under the Drugs and Cosmetics Act,1940.

3. This licence shall, unless previously suspended or revoked, be in force for a period of one year from the date specified below:–

4. Details of the new drug to be manufactured

Name:	
Quantity:	

Place: …….

Central Licencing Authority and Stamp

Date: .....

Annexure:

Details of unapproved new drug manufactured:

Serial number	Date of manufacture	Licence number	Name of the unapproved new drug	Quantity manufactured	Manufactured for

Details of record of patient history:

Licence number	Name of the new drug	Patient name	Diagnosis detail with date	Disease name	Dosage schedule

Details of reconciliation of unapproved active pharmaceutical ingredient manufactured:

Date	Name of the unapproved new drug	Licence No.	Quantity manufactured	Quantity supplied	Quantity remained	Supplied to	Quantity – left over or remain unused or got damaged or expired or found of sub-	Action taken

							standard quality	

*** Write NA where not applicable.**

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Dr. MANDEEP K. BHANDARI, Jt. Secy.

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