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.