[1][SCHEDULE Y

(See rules 122A, 122B, 122D, 122DA, 122DAA and 122E)

REQUIREMENTS AND GUIDELINES FOR PERMISSION TO IMPORT AND / OR MANUFACTURE OF NEW DRUGS FOR SALE OR TO UNDERTAKE CLINICAL TRIALS

1. Application for permission.- (1) Application for permission to import or manufacture new drugs for sale or to undertake clinical trials shall be made in Form 44 accompanied with following data in accordance with the appendices, namely:-

(i) chemical and pharmaceutical information as prescribed in item 2 of Appendix I;

(ii) animal pharmacology data as prescribed in item 3 of Appendix I and Appendix IV;

(a) specific pharmacological actions as prescribed in item 3.2 of Appendix I, and demonstrating, therapeutic potential for humans shall be described according to the animal models and species used. Wherever possible, dose-response relationships and ED_{50s} shall be submitted. Special studies conducted to elucidate mode of action shall also be described (Appendix IV);

(b) general pharmacological actions as prescribed in item 3.3 of Appendix I and item 1.2 of Appendix IV;

(c) pharmacokinetic data related to the absorption, distribution, metabolism and excretion of the test substance as prescribed in item 3.5 of Appendix I. Wherever possible, the drug effects shall be corelated to the plasma drug concentrations;

(iii) animal toxicology data as prescribed in item 4 of Appendix I and Appendix III;

(iv) human Clinical Pharmacology Data as prescribed in items 5, 6 and 7 of Appendix I and as stated below:-

(a) for new drug substances discovered in India, clinical trials are required to be carried out in India right from Phase I and data should be submitted as required under items 1, 2, 3, 4, 5 (data, if any, from other countries), and 9 of Appendix I;

(b) for new drug substances discovered in countries other than India, Phase I data as required under items 1, 2, 3, 4, 5 (data from other countries) and 9 of Appendix I should be submitted along with the application. After submission of Phase I data generated outside India to the Licensing Authority, permission may be granted to repeat Phase I trials and/or to conduct Phase II trials and subsequently Phase III trials concurrently with other global trials for that drug. Phase III trials are required to be conducted in India before permission to market the drug in India is granted;

(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 Phase(s);

(d) application for permission to initiate specific phase of clinical trial should also accompany Investigator's brochure, proposed protocol (Appendix X), case record form, study subject's informed consent document(s) (Appendix V), investigator's undertaking (Appendix VII) and ethics committee clearance, if available (Appendix VIII);

---

1. Subs. G.S.R. 32(E), dt. 20.1.2005.

(e) reports of clinical studies submitted under items 5-8 of Appendix I should be in consonance with the format prescribed in Appendix II of this 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 as undertaken, and express agreement with the conclusions. Each page should be numbered;

(v) regulatory status in other countries as prescribed in item 9.2 of Appendix I, 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. (item 9.2 of Appendix I). 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 Licensing 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 as prescribed in item 10 of Appendix I. The prescribing information (package insert) shall comprise the following sections: generic name; composition; dosage form/s, indications; dose and method of administration; use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.); contra-indications; warnings; precautions; drug interactions; undesirable effects; overdose; pharmacodynamic and pharmacokinetic properties; incompatibilities; shelf-life; packaging information; storage and handling instructions. 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 rules 96 and 97. After submission and approval by the Licensing Authority, no changes in the package insert shall be effected without such changes being approved by the Licensing Authority; and

(vii) complete testing protocol/s for quality control testing together with a complete impurity profile and release specifications for the product as prescribed in item 11 of Appendix I 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.

(2) If the study drug is intended to be imported for the purposes of examination, test or analysis, the application for import of small quantities of drugs for such purpose should also be made in Form 12.

(3) For drugs indicated in life threatening / serious diseases or diseases of special relevance to the Indian health scenario, the toxicological and clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority.

2. Clinical Trial:

(1) *Approval for clinical trial*

(i) Clinical trial on a new drug shall be initiated only after the permission has been granted by the Licensing Authority under rule 21 (b), and the approval obtained from the respective ethics committee (s). The Licensing Authority as defined shall be informed of the approval of the respective institutional ethics committee(s) as prescribed in Appendix VIII, and the trial initiated at each respective site only after obtaining such an approval for that site. The trial site(s) may accept the approval granted to the protocol by the ethics committee of another trial site or the approval granted by an independent ethics committee (constituted as per Appendix VIII), provided

that the approving ethics committee(s) is/are willing to accept their responsibilities for the study at such trial site(s) and the trial site(s) is/are willing to accept such an arrangement and that the protocol version is same at all trial sites.

(ii) All trial Investigator(s) 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. If services of a laboratory or a facilities outside the country are to be availed, its/their name(s), address(s) and specific services to be used should be stated in the protocol to avail Licensing Authority's permission to send clinical trial related samples to such laboratory(ies) and/or facility(ies). In all cases, information about laboratory(ies) / facilities to be used for the trial, if other than those at the investigation site(s), should be furnished to the Licensing Authority prior to initiation of trial at such site(s).

(iii) Protocol amendments if become necessary before initiation or during the course of a clinical trial, all such amendments should be notified to the Licensing Authority in writing along with the approval by the ethics committee which has granted the approval for the study. No deviations from or changes to the protocol should be implemented without prior written approval of the ethics committee and the Licensing Authority except when it is necessary to eliminate immediate hazards to the trial Subject(s) or when change(s) involve(s) only logistic or administrative aspects of the trial. All such exceptions must be immediately notified to the ethics committee as well as to the Licensing Authority. Administrative and/or logistic changes in the protocol should be notified to the Licensing Authority within 30 days.

(2) *Responsibilities of 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 Practice (GCP) Guidelines issued by the Central Drugs Standard Control Organization, Directorate General of Health Services, Government of India as well as with all applicable statutory provisions. Standard operating procedures should be documented to ensure compliance with GCP and applicable regulations.

(ii) Sponsors are required to submit a status report on the clinical trial to the Licensing 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 (Appendix XI), if any, and the reason for discontinuation of the study or non-pursuit of the new drug application;

[1][(iv) Any report of the serious adverse event, after due analysis shall be forwarded by the sponsor to the Licensing Authority as referred to in clause (b) of rule 21, the Chairman 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.]

[2][(v) in case of injury or death occurring to the clinical trial subject, the Sponsor (whether a pharmaceutical company or an Institution) or his representative, whosoever, had obtained permission from the Licensing Authority for conduct of the clinical trial, shall make payment for medical management of the subject and also provide financial compensation for the clinical trial related injury or death in the manner as prescribed in Appendix XII;

[2][(vi) the Sponsor (whether a pharmaceutical company or an Institution) or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial, shall submit details of compensation provided or paid for clinical trial related injury or death, to the Licensing Authority within thirty days of the receipt of the order of the Licensing Authority.]

---

1. Subs. by G.S.R. 889(E) dated 12-12-2014

2. Ins. By G.S.R. 53(E) dated 30-1-2013

[1][(3)(i)] *Responsibilities of the Investigator(s)*:

The Investigator(s) shall be responsible for the conduct of the trial according to the protocol and the GCP Guidelines and also for compliance as per the undertaking given in Appendix VII. Standard operating procedures are required to be documented by the investigators for the tasks performed by them. During and following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided to the participant for any adverse events. Investigator(s) shall report all serious and unexpected adverse events to the [2][Licensing Authority defined under clause (b) of rule 21, the Sponsor or his repeesentative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial, and the Ethics Committee that accorded approval to the study protocol, within twenty four hours of their occurance. [3][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 Licensing 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 Licensing Authority as referred to in clause (b) of rule 21, the Chairman 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.]].

[4][(ii)The Investigator shall provide information to the clinical trial subject through informed consent process as provided in Appendix V about 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 or his/her nominees(s) of their rights to contact the Sponsor or his representative whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial for the purpose of making claims in the case of trial related injury or death.]

(4) *Informed Consent*:

(i) 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 non-technical and understandable by the study subject. 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 Licensing Authority. Any changes in the informed consent documents should be approved by the ethics committee and submitted to the Licensing Authority before such changes are implemented.

(ii) 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 authorize an intervention in the patient as provided by the law(s) of India). If the Subject or his/her legally acceptable representative is unable to read/write – an impartial witness should be present during the entire informed consent process who must append his/her signatures to the consent form.

(iii) 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 study Subjects is given in Appendix V.

---

1. Sub-para (3) renumbered as sub-para, (3)(i) thereof by G.S.R 53(E), dated 30-01-2013.
2. Subs. by G.S.R. 53(E), dated 30-01-2013.
3. Subs. by G.S.R. 889(E), dated 12-12-2014.
4. Ins. by G.S.R. 53(E), dated 30-01-2013.

(5) *Responsibilities of the 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. 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, umemployed or impoverished persons, patients in emergency situation, ethnic minority groups, homeless persons, nomads, refugees, minors or others incapable of personally giving consent. Ethics committee(s) should get document 'standard operating procedures' and should maintain a record of its proceedings.

(ii) Ethics Committee(s) should make, at appropriate intervals, an ongoing review of the trials for which they review the protocol(s). Such a review may be based on the periodic study progress reports furnished by the investigators and/or monitoring and internal audit reports furnished by the Sponsor and/or by visiting the study sites.

(iii) 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 Licensing Authority.

[1][(iv) In case of serious adverse event occurring to the clinical trial subject, the Ethics Committee shall forward its report on the serious adverse event, after due analysis, along with its opinion on the financial compensation, if any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority as referred to in clause (b) of rule 21 for conducting the clinical trial, to the Licensing Authority within thirty days of the occurrence of the serious adverse event.

[2][5(A). *Serious Adverse Events*:

(1) A serious adverse event is an untoward medical occurrence during clinical trial that is associated with death, in patient hospitalization (in case the study was being conducted on out-patient), prolongation of hospitalization (in case the study was being conducted on in-patient), persistent or significant disability or incapacity, a congenital anomaly or birth defect or is otherwise life threatening.

(2) The Investigator shall report all serious [3][***] adverse events to the Licensing Authority as defined under clause (b) of Rule 21, the Sponsor or his representative, whosoever had obtained permission from the Licensing 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 as per Appendix XI and the said Licensing Authority shall determine the cause of injury or death as per the procedure prescribed under Appendix XII and pass orders as deemed necessary. [4][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 Licensing Authority along with the report of the serious adverse event.

---

1. Subs. by G.S.R. 889(E) dated 12-12-2014.
2. Ins. by G.S.R. 53(E) dated 30-01-2013.
3. The words "and unexpected"omitted by G.S.R. 889(E) dated 12-12-2014.
4. Ins. by G.S.R. 889 (E) dated 12-12-2014.

(6) *Human Pharmacology (Phase I)*:

(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 human(s). Studies in this Phase of development usually have non-therapeutic objectives and may be conducted in healthy volunteers subjects or certain types of patients. Drugs with significant potential toxicity e.g. cytotoxic drugs are usually studied in patients**.** Phase I trials should preferably be carried out by Investigators trained in clinical pharmacology with access to the necessary facilities to closely observe and monitor the Subjects.

(ii) 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., characterization 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/ 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.

(7) *Therapeutic exploratory trials (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(s) 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.

(iii) If the application is for conduct of clinical trials as a part of multi-national clinical development of the drug, the number of sites and the patients as well as the justification for undertaking such trials in India shall be provided to the Licensing Authority.

(8) *Therapeutic confirmatory trials (Phase III)*:

(i) Phase III studies have primary objective of demonstration or confirmation of therapeutic benefit(s). 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 drug(s).

(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 need to be carried out 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, Licensing 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.

(iv) 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 Licensing Authority along with the application.

(9) *Post Marketing Trials (Phase IV)*:

Post Marketing trials are studies (other than routine surveillance) performed after drug approval and related to the approved indication(s). These trials go beyond the prior demonstration of the drug's safety, efficacy and dose definition. These trials may not be considered necessary at the time of new drug approval but may be required by the Licensing Authority for optimizing the drug's use. They may be of any type but should have valid scientific objectives. Phase IV trials include additional drug-drug interaction(s), dose-response or safety studies and trials designed to support use under the approved indication(s), e.g. mortality/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. Any claim sought to be made for the drug product that is not based on data submitted under preceding items of this Schedule should be supported by studies included under this item of the Schedule (Appendix I, item 8.3).

(1) *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.

(2) *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 surveliance 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

(c) 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) Paediatric Subjects are legally unable to provide written informed consent, and are dependent on their parent(s)/ legal guardian to assume responsibility for their participation in clinical studies. Written informed consent should be obtained from the parent/ 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. 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. 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(s)/ legal guardian, the welfare of a pediatric patient would be jeopardized by his or her failing to participate in the study. In this situation, continued parental/ legal guardian consent should be sufficient to allow participation in the study.

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

(3) *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/nursing women or foetuses/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) *Post Marketing Surveillance*:

(i) The applicant shall have a pharmacovigilance system in place for collecting, processing and forwarding the report to the licensing authority for information on adverse drug reactions emerging from the use of the drug manufactured or marketed by the applicant in the country.

(ia) The 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.

(ib) Subsequent to approval of the product, new drug shall be closely monitored for its clinical safety once it is marketed.

(ic) The applicant shall furnish Periodic Safety Update Reports (PSURs) in order to-

(a) report all the relevant new information from appropriate sources;

(b) relate these data to patient exposure ;

(c) summarize the market authorization status in different countries and any significant variations related to safety; and

(d) indicate whether changes should be made to product information in order to optimize the use of the product.

(ii) Ordinarily all dosage forms and formulations as well as indications for new drugs should be covered in one PSUR. Within the single PSUR 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 PSURs 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 PSURs need to be submitted annually. Licensing authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health. PSURs due for a period must be submitted within 30 calendar days of the last day of the reporting period.

However, all cases involving serious unexpected adverse reactions must be reported to the licensing authority within 15 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 PSURs.

---

1. Subs. by G.S.R. 287(E) dated 08-03-2016.

(v) A PSUR should be structured as follows:

(a) A title page stating: Periodic safety update report for the product, applicant's name, period covered by the report, date of approval of new drug, date of marketing of new drug and date of reporting;
(b) Introduction,
(c) Current worldwide market authorization status,
(d) Update of actions taken for safety reasons,
(e) Changes to reference safety information,
(f) Estimated patient exposure,
(g) Presentation of individual case histories,
(h) Studies,
(i) Other information,
(j) Overall safety evaluation,
(k) Conclusion,
(l) Appendix providing material relating to indications, dosing, pharmacology and other related information.

(5) *Special studies: Bioavailability / Bioequivalence Studies*:

(i) 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.

(ii) 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.

(iii) Dissolution and bioavailability data submitted with the new drug application must provide information that assures bioequivalence or establishes bioavailability and dosage correlations between the formulation(s) sought to be marketed and those used for clinical trials during clinical development of the product. (See items 8.1, 8.2 and 8.3 of Appendix I).

(iv) All bioavailability and bioequivalence studies should be conducted according to the Guidelines for Bioavailability and Bioequivalence studies as prescribed.

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 (as defined under rule 122-E) prior to the permission for sale. Depending upon the nature of new drugs and disease(s), additional information may be required by the Licensing Authority. The applicant shall certify the authencity of the data and documents submitted in support of an application for new drug. The Licensing Authority reserves the right to reject any data or any document(s) if such data or contents of such documents are found to be of doubtful integrity.

APPENDIX I

DATA TO BE SUBMITTED ALONG WITH THE APPLICATION TO CONDUCT CLINICAL TRIALS/IMPORT/MANUFACTURE OF NEW DRUGS FOR MARKETING 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 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/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 Appendix IX)
Final release specification
Reference standard characterization
Material safety data sheet

2.7. Data on Formulation
Dosage form
Composition
Master manufacturing formula
Details of the formulation (including inactive ingredients)
In process quality control check
Finished product specification
Excipient compatibility study
Validation of the analytical method
Comparative evaluation with international brand(s) or approved Indian brands, if applicable
Pack presentation
Dissolution
Assay
Impurities
Content uniformity
pH
Force degradation study
Stability evaluation in market intended pack at proposed storage conditions
Packing specifications

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 nos. 2.1, 2.3, 2.6, 2.7) are required.

3. Animal Pharmacology (for details refer Appendix IV)

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 Appendix III)

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/Hypersensitivity
4.7. Genotoxicity
4.8. Carcinogenicity

[1][**Note.-** Where the data on animal toxicity as per the specifications of Appendix III has 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 / 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(s) as given in Appendix II

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 / Bio-equivalence.
8.3. Other studies e.g. geriatrics, paediatrics, pregnant or nursing women

1. Subs. by G.S.R. 313(E) dated 16-03-2016.

9. Regulatory status in other countries

9.1. Countries where the drug is

a. Marketed

b. Approved

c. Approved as 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

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 Licensing Authority), with testing protocol/s, full impurity profile and release specifications.

NOTES:

(1) All items may not be applicable to all drugs. For explanation, refer text of Schedule Y.

(2) For requirements of data to be submitted with application for clinical trials refer text of this Schedule.

APPENDIX IA

DATA REQUIRED TO BE SUBMITTED BY AN APPLICANT FOR GRANT OF PERMISSION TO IMPORT AND / 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 Outline of the method of manufacture of active ingredients

2.6 Stability data

3. Marketing information

3.1 Proposed package insert / promotional literature

3.2 Draft specimen of the label and carton

4. Special studies conducted with approval of Licensing Authority

4.1 Bioavailability / Bioequivalence and comparative dissolution studies for oral dosage forms

4.2 Sub-acute animal toxicity studies for intravenous infusions and injectables

APPENDIX II

STRUCTURE, CONTENTS AND FORMAT FOR CLINICAL STUDY REPORTS

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 summarize the important conclusions derived from the study.

3. Statement of compliance with the 'Guidelines for Clinical Trials on Pharmaceutical Products in India :

GCP Guidelines' issued by the Central Drugs Standard Control Organization, Ministry of Health, Government of India.

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 date(s) of approvals of trial documents for each of the participating sites should be provided. A declaration should state that EC notifications as per Good Clinical Practice Guidelines issued by Central Drugs Standard Control Organization 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/ 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 / randomization techniques if any, allowed/ 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 A l l serious adverse events, whether expected or unexpected and

13.2 unexpected advese events whether serious or not (compiled from data received as per Appendix XI).

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 Trial Report

(a) Protocol and amendments
(b) Specimen of Case Record Form
(c) Investigators' name(s) 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) CRFs 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's certificate that he/she has read the report and that the report accurately describes the conduct and the results of the study.

APPENDIX III

ANIMAL TOXICOLOGY (NON-CLINICAL TOXICITY STUDIES)

1. General Principles:

Toxicity studies should comply with the norms of Good Laboratory Practice (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 characterized 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 5 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 Appendix I item 4.2) 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 7 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. LD10 and LD50 should be reported preferably with 95 percent confidence limits. If LD50s 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, MTD should be established in non-rodent species.

1.1.2 Repeated-dose Systemic Toxicity Studies: These studies (see Appendix I, item 4.2) 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 (see item 1.8). If a species is known to metabolize 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 7 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, is shown in Item 1.9.

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 behavioral, 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 5 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 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 5 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 behaviour 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 MTD study. Dosing should start after initial recording of cage-side and laboratory parameters. Starting dose may be 3 to 5 times the extrapolated effective dose or 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/water intake, blood biochemistry, haematology, and gross and microscopic studies of all viscera and tissues.

(iv) 90-Day 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 behaviour 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 and/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 4 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 or 28-day 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 6 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 (see Appendix I, item 4.4) 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 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/ parturition periods, length of gestation, parturition, post-partum 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/ visceral/ 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 4 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 F_1 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 F_1 generation should thus be evaluated to obtain the F_2 generation whose growth parameters should be monitored till weaning. The criteria of evaluation should be the same as described earlier (3.4.1).

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/ 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 (see Appendix I, item 4.5) 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 and/ or vehicle control, preferably use of 2 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 should be done in rabbit and rat. 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 7 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/ 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 8 animals should screen 4 concentrations (patch application for 2 hours ±15 min.) with and without UV exposure (10 J/cm2). Observations recorded at 24 and 48 hours should be used to ascertain highest nonirritant dose. Main test should be performed with 10 test animals and 5 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 7 days (more according to clinical use), subject to a maximum of 30 days. Observation parameters should include swelling, closure of introitus 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 7 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 and/or mucus in faeces, condition of anal region/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. 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 that 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/ 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 nonirritant and minimum irritant doses, and second, the main test. The initial study will also have two components. To determine the intradermal induction dose, 4 dose levels should be tested by the same route in a batch of 4 male and 4 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 2 males and 2 females. A minimum of 6 male and 6 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 (day 21) should be done. If there is no response, re-challenge should be done 7-30 days 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 nonirritant 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 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 lymphoma tic assay.

(iii) An *in vivo* test for chromosomal damage using rodent haematopoietic cells. Other genotoxicity tests e.g. tests for measurement of DNA adducts, DNA strand breaks, 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.

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 CA in rodent bone marrow. Data analysis of CA should include analysis of 'gaps.'

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.

(i) 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.

(ii) *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 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.

(iii) *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 1 and 2 of study followed by sacrifice of animals 6 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-MayGruenwald staining should be done and increased number of micronuclei in polychromatic erythrocytes (minimum 1000) should be used as the evaluation criteria.

(iv) 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 1 followed by intra-peritoneal colchicine administration at 22 hours. Animals should be sacrificed 2 hours after colchicine administration. Bone marrow from both the femora should be taken out, flushed with hypotonic saline (20 min.), 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 (see Appendix I, item 4.8)*

Carcinogenicity studies should be performed for all drugs that are expected to be clinically used for more than 6 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 metabolite(s) results in local tissue reactions or other pathophysiological responses. For pharmaceuticals developed to treat certain serious diseases, Licensing 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 / are 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 7 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 atleast 50 animals of each sex. A high dose sattelite group for evaluation of pathology other than

neoplasia should contain 20 animals of each sex while the sattelite control group should contain 10 animals 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
[1][Oral or Parenteral or Transdermal	Single dose or several doses in one day, Upto 1wk	I,II,III	2sp,2wks
	> 1 wk but upto 2wks	I,II,III	2sp;4wks
	Upto 2 wks	Marketing permission	2sp;4wks
	> 2 wk but upto 4wks	I,II,III	2 sp; equal to duration of human exposure
		Marketing permission	2 sp; 12 wks
	> 4 wks but upto 12 wks	I,II,III	2 sp; equal to duration of human exposure
		Marketing permission	2sp;24wks
	> 12 wks but upto 24 wks	I,II,III	2 sp; equal to duration of human exposure
		Marketing permission	2 sp; Rodent 24 wks, non-rodent 36 wks
	> 24 wks	I,II,III	2 sp; Rodent 24 wks, non-rodent 36 wks
		Marketing permission	2 sp; Rodent 24 wks, non-rodent 36 wks]
Inhalation (general anaesthetics, aerosols)	Upto 2 wk	I,II,III 3h/d, 5d/wk)	2sp;1mo; (Exposure time
	Upto 4wk	I,II,III	2sp;12wk, (Exposure time 6h/d, 5d/wk)
	> 1 4wk	I,II,III	2sp;24wk, (Exposure time 6h/d, 5d/wk)
Local Toxicity Studies Dermal	Upto 2 wk	I,II,	1sp;4wk
		III	2sp;4wk
	> 2 wk	I,II,III	2sp;12wk
Ocular or Otic or Nasal	Upto 2 wk	I,II	1sp;4wk
		III	2sp;4wk
	> 2 wk	I,II,III	2sp;12wk
Vaginal or Rectal	Upto 2 wk	I,II	1sp;4wk
		III	2sp;4wk
	> 2 wk	I,II,III	2sp;12wk

1. Subs. by G.S.R. 287(E), dt. 08.3.2016.

Male Fertility Study:

- [1][Phase III in male volunteers/patients]

Female Reproduction and Developmental 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/Hypersensitivity: Phase I, II, III - when there is a cause of concern or for parenteral drugs (including derrmal 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

Arcinogenicity:

- Phase III - when there is a cause for concern, or when the drug is to be used for more than 6 months.

Abbreviations: sp-species; mo-month; wk-week; d -day; h-hour; I, II, III - Phases of clinical trial;

Note:

1. Animal toxicity data generated in other countries may be accepted and may not be asked to be repeated/duplicated in India on a case to case basis depending upon the quality of data and the credentials of the laboratory(ies) where such data has been generated.
2. Requirements for fixed dose combinations are given in Appendix VI.

1.9 *Number of animals required for repeated-dose toxicity studies*

Group	14-28 days				84-182 days			
	Rodent (Rat)		Non-rodent (Dog or Monkey)		Rodent (Rat)		Non-rodent (Dog or Monkey)	
	M	F	M	F	M	F	M	F
Control	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6
Low dose	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6
Intermediate dose	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6
High dose	6-10	6-10	2-3	2-3	15-30	15-30	4-6	4-6

1. Subs. by G.S.R. 287(E), dt. 08.3.2016.

2.0 *Laboratory parameters to be included in toxicity studies.*

Haematological parameters

• Haemoglobin	• Total RBC Count	• Haematocrit	• Reticulocyte Count
• Total WBC Count	• Differential WBC Count	• Platelet Count	Terminal Bone Marrow Examination
• ESR (Non-rodents only)	• General Blood Picture: A special mention of abnormal and 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-hour urinary output
• Reaction (pH)	• Albumin	•Sugar	• Acetone
Bile pigments	Urobilinogen	• Occult Blood	
• Microscopic examination of urinary sediment.			

Blood Biochemical Parameters

• Glucose	• Cholesterol	• Triglycerides	• HDL Cholesterol (Non-rodents only)
• LDL Cholesterol (Non-rodents only)	• Bilirubin	• SGPT (ALT)	• SGOT (AST)
• Alkaline Phosphatase (ALP)	• GGT (Non-rodents only)	• Blood Urea Nitrogen	• Ceatinine
• 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 IND needed for the conduct of different phases of clinical trials.

Note: Refer Appendix III (Points 1.1 through 1.7 and tables 1.8 and 1.9) 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 toxicity studies

(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/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 an agent 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 the non- 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/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/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.

APPENDIX IV
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 and/or pathophysiological effects observed in toxicology and/or clinical studies; and to investigate the mechanism of the adverse pharmacodynamic effects observed and/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

test(s) 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 i*n 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, behavioral 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 hemoglobin 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 behavioral 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.

APPENDIX V

INFORMED CONSENT

1. Checklist for study Subject's informed consent documents

1.1 Essential Elements:

1. Statement that the study involves research and explanation of the purpose of the research
2. Expected duration of the Subject's participation.
3. Description of the procedures to be followed, including all invasive procedures and
4. Description of any reasonably foreseeable risks or discomforts to the Subject
5. 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.
6. Disclosure of specific appropriate alternative procedures or therapies available to the Subject.
7. 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
8. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials)
9. Compensation and/or treatment(s) available to the Subject in the event of a trial-related injury
10. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury
11. The anticipated prorated payment, if any, to the Subject for participating in the trial
12. Subject's responsibilities on participation in the trial
13. 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
14. Any other pertinent information

1.2 Additional elements, which may be required

(a) Statement of foreseeable circumstances under which the Subject's participation may be terminated by the Investigator without the Subject's 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) 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 fetus, 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: _____

		Please 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 purpose(s)	[ ]
(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: _____

[1][Copy of the Patient Information Sheet and duly filled Informed Consent Form shall be handled over to the subject or his/her attendant.]

1. Ins. by G.S.R 53(E), dt. 30-01-2013.

APPENDIX VI

FIXED DOSE COMBINATIONS (FDCs)

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

(a) The first group of FDCs includes those in which one or more of the active ingredients is a new drug. For such FDCs to be approved for marketing data to be submitted will be similar to data required for any new drug (including clinical trials) [see rule 122E, item (a)].

(b)(i) The second group FDCs includes those in which active ingredients already approved/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 [see rule 122E, item (c)]. If clinical trials have been carried out with the FDC in other countries, reports of such trials should be submitted. If the FDC is marketed abroad, the regulatory status in other countries should be stated. (see Appendix I, item 9).

(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 an 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 FDCs, clinical trials may be required. For obtaining permission to carry out clinical trials with such 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 (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 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 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 FDC includes those whose individual active ingredients (or drugs from the same class) have been widely used in a particular indication(s) 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 FDCs, and marketing permission may be granted if the FDC has an acceptable rationale.

APPENDIX VII

UNDERTAKING BY THE INVESTIGATOR

1. Full name, address and title of the Principal Investigator (or Investigator(s) 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, and / or any other statement(s) of qualification(s))

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 investigation (s).

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 / favorable opinion from the Ethics Committee of the amendment, except where necessary to eliminate an immediate hazard(s) to the trial Subjects or when the change(s) involved are only logistical or administrative in nature.

(iii) I agree to personally conduct and/or supervise the clinical trial at my site.

(iv) I agree to inform all Subjects, 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 GCP 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 and GCP 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 / inspection by the Sponsor, Ethics Committee, Licensing Authority or their authorized representatives, in accordance with regulatory and GCP provisions. I will fully cooperate with any study related audit conducted by regulatory officials or authorized 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 unexpected serious adverse events to the Sponsor as well as the Ethics Committee within seven days of their occurence.

(xi) I will maintain confidentiality of the identification of all participating study patients and assure security and confidentiality of study data.

(xii) 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

APPENDIX VIII

ETHICS COMMITTEE

1. The number of persons in an Ethcis Committee should have atleast seven members. Ethics Committee should appoint, from among its members, a Chairperson (who is from outside the institution) and a Member Secretary. Other members should be a mix of medical/non-medical, scientific and non-scientific persons, including lay public, to reflect the different viewpoints.

For review of each protocol the quorum of Ethics Committee should be atleast 5 members with the following representations:

(a) basic medical scientists (preferably one pharmacologist).

(b) clinicians

(c) legal expert

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

(e) lay person from the community.

In any case, the ethics committee must include at least one member whose primary area of interest / specialization is nonscientific and at least one member who is independent of the institution / trial site. Besides, there should be appropriate gender representation on the Ethics Committee. If required, Subject experts may be invited to offer their views. Further, based on the requirement of research area, e.g. HIV AIDS, genetic disorders etc. specific patient groups may also be represented in the Ethics Committee as far as possible.

Only those Ethics Committee members who are independent of the clinical trial and the Sponsor of the trial should vote / provide opinion in matters related to the study.

2. Format for Approval of Ethics Committee

To

Dr.

Dear Dr. _____

The Institutional Ethics Committee / 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 and/or vernacular language.

(c) Investigator's Brochure, dated_____, Version no._____

(d) Proposed methods for patient accrual including advertisement (s) etc. proposed to be used for the purpose.

(e) Principal Investigator's current CV.

(f) Insurance Policy / Compensation for participation and for serious adverse events occurring during the study participation.

(g) Investigator's Agreement with the Sponsor.

(h) Investigator's Undertaking (Appendix VII).

The following members of the ethics committee were present at the meeting held on (date, time, place).

_____ Chairman 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 Institutional Ethics Committee / Independent Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

Yours sincerely,

Member Secretary, Ethics Committee.

APPENDIX IX

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, and/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 12 months' duration 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 6 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(es) 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/65% RH ± 5% RH	12 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

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.

(ii) 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	12 months
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 months

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

Study	Study conditions	Duration of study
Long term	- 20°C ± 5°C	12 months

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

(v) Stability testing of the formulation 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.

APPENDIX X

CONTENTS OF THE PROPOSED PROTOCOL FOR CONDUCTING CLINICAL TRIALS

1. Title Page

(a) Full title of the clinical study,

(b) Protocol / Study number, and protocol version number with date

(c) The 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(s) of clinical laboratories and other departments and/or facilities participating in the study.

2. Table of Contents

A complete Table of Contents including a list of all Appendices.

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(s) (primary as well as secondray) 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 dropouts would be managed and if they would be replaced, describe the method of handling of protocol waivers, if any. The person(s) 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 non-compliance 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) *Unblinding procedures*: If the study is blinded, the circumstances in which unblinding may be done and the mechanism to be used for unblinding should be given.

10. Adverse Events (See Appendix XI): 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 specifics required in filling out the forms CRF correction requirements, including who is authorized to make corrections on the CRF 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/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 analyzed and reported along with the description of statistical tests to be used to analyze 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 Appendix VII).

16. Appendices: Provide a study synopsis, copies of the informed consent documents (patient information sheet, informed consent form etc.); CRF and other data collection forms; a summary of relevant pre-clinical safety information and any other documents referenced in the clinical protocol.

APPENDIX XI

Data Elements for reporting serious adverse events occuring in a clinical trial

1. Patient Details

Initials & other relevant identifier (hospital/OPD record number etc.)* Gender
Age and/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/OTC drugs) and non-drug therapies, as for the suspected drug(s).

4. Details of Suspected Adverse Drug Reaction(s)

Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious. In addition to a description of the reported signs and symptoms, whenever possible, describe a specific diagnosis for the reaction.*

Start date (and time) of onset of reaction.

Stop date (and time) or duration of reaction.

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 and/or treatment that may have been conducted.

For a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction; 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

Address

Telephone number

Profession (speciality)

Date of reporting the event to Licensing Authority:

Date of reporting the event to Ethics Committee overseeing the site:

Signature of the Investigator

Note: Information marked * must be provided."]

[1][APPENDIX XII
Compensation in case of injury or death during clinical trial

[2][(1) 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.]

(2) In case the injury occurring to the trial subject is related to the clinical trial, such subject shall also be entitled for financial compensation as per order of the Licensing Authority defined under clause (b) of Rule 21 and the financial compensation will be over and above any expenses incurred on the medical management of the subject. [3][In case, there is no permanent injury, the quantum of compensation shall be commensurate with the nature of the non-permanent injury and loss of wages.]

(3) In the case of clinical trial related death of the subject, his/her nominee(s) would be entitled for financial compensation as per the order of the Licensing Authority defined under clause (b) of Rule 21, and the financial compensation will be over and above any expenses incurred on the medical management of the subject.

(4) The financial compensation for clinical trial related injury or death could be in the form of:-

(a) Payment for medical management;
(b) Financial compensation for trail related injury;
(c) Financial compensation to nominee(s) of the trial subject in case of death;
(d) Financial compensation for the child injured in–utero because of the participation of parent in clinical trial.

(5) The Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conduct of the clinical trial shall provide financial compensation, if the injury or death has occurred because of any or the following reasons, namely:-

(a) Adverse effect of investigational product(s);
(b) Any clinical trial procedures involved in the study;
(c) Violation of the approved protocol, scientific misconduct or negligence by the Sponsor or his representative or the Investigator;
(d) Failure of investigational product to provide intended therapeutic effect; where, the standard care, though available, was not provided to the subject as per the clinical trial protocol.
(e) Use of placebo in a placebo-controlled trial, where, the standard care, though available, was not provided to the subject as per the clinical trial protocol;

---

1. Ins. by G.S.R. 53(E), dt. 30.1.2013.
2. Subs. by G.S.R. 889(E), dt. 12.12.2014.
3. Ins. by G.S.R. 889(E), dt. 12.12.2014.

(f) Adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol;

(g) Injury to the child in-utero because of the participation of parent in clinical trial.

(6) Procedure for payment of financial compensation.

(a) The Investigator shall report all serious [1][***] adverse events to the Licensing Authority as defined under clause (b) of Rule 21, the Sponsor or his representative whosoever had obtained permission from the Licensing 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 as per Appendix XI. [2][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 Licensing Authority along with the report of the serious adverse event.]

(b) (i) The cases of serious adverse events of death shall be examined as under:

(A) An independent Expert Committee shall be constituted by the Licensing Authority as defined under Rule 21(b) to examine the cases and recommend to the Licensing Authority for the purpose of arriving at the cause of death and quantum of compensation in case of clinical trial related death.

(B)The Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conducting the clinical trial and the Investigator shall forward their reports on serious adverse event of death after due analysis to [3][***] the Licensing Authority as defined under Rule 21(b) and the head of the Institution where the trial has been conducted within [4][fourteen days] of occurrence of the serious adverse event of death.

(C) The Ethics Committee shall forward its report on serious adverse event of death after due analysis along with its opinion on the financial compensation, if any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority as defined under Rule 21(b) for conducting the clinical trial, [5][***] to the Licensing Authority within [6][thirty days] of the occurrence of the serious adverse event of death.

[2][(CA) The Licensing Authority shall forward the report of the Investigator, Sponsor or his representative whosoever had obtained permission from the Licensing Authority for conducting clinical trial and the Ethics Committee to the Chairman of the Expert Committee.

---

1. The word "and unexpected" omitted by G.S.R. 889(E), dt. 12.12.2014.
2. Ins. by G.S.R. 889(E), dt. 12.12.2014.
3. The word "Chairman of the Expert Committee with a copy of the report to" omitted by G.S.R. 889(E), dt. 12.12.2014.
4. Subs. by G.S.R. 889(E), dt. 12.12.2014.
5. The word "to the Chairman of the Expert Committee with a copy of the report" omitted by G.S.R. 889(E), dt. 12.12.2014.
6. Subs. by G.S.R. 889(E), dt. 12.12.2014.

(D) The Expert Committee shall examine the report of serious adverse event of death and give its recommendations to the Licensing Authority for the purpose of arriving at the cause of the adverse event with in [1][one hundred and five days of the occurrence of the adverse event,] and the expert committee while examining the event, may take into consideration, the reports of the Investigator, Sponsor or his representative whosoever had obtained permission from the Licensing Authority for conducting the clinical trial and the Ethics Committee.

(E) In the case of clinical trial related death, the Expert Committee shall also recommend the quantum of compensation to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority as defined under Rule 21(b) for conducting the clinical trial.

(F) The Licensing Authority shall consider the recommendations of the Expert Committee and shall determine the cause of death and pass orders as deemed necessary.

(G) In case of clinical trial related death, the Licensing Authority, after considering the recommendations of the Expert Committee, shall decide the quantum of compensation to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conducting the clinical trial and shall pass orders as deemed necessary within [1][one hundred and fifty days of the occurrence of the adverse event].

(ii) Cases of serious adverse events, other than deaths, shall be examined as under:

(A) The Sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conducting the clinical trial, and the Investigator shall forward their reports on serious adverse event, after due analysis, to the Licensing Authority as defined under Rule 21(b), Chairman of the Ethics Committee and the head of the Institution where the trial has been conducted within [1][fourteen days] of occurrence of the serious adverse event.

(B) The Ethics Committee shall forward its report on the serious adverse event, after due analysis along with its opinion regarding the financial compensation, if any, to be paid by the Sponsor or his representative, whosoever had obtained permission from the Licensing Authority as defined under Rule 21(b) for conducting the clinical trial, to the Licensing Authority within [1][thirty days] of occurrence of the serious adverse event.

(C) The Licensing Authority shall determine the cause of injury and pass order as deemed necessary. The Licensing Authority shall have the option to constitute an independent Expert Committee, wherever

---

1. Subs. by G.S.R. 889(E), dt. 12.12.2014.

considered necessary, to examine such serious adverse events of injury, which will recommend to the Licensing Authority for arriving at the cause of the injury and also the quantum of compensation in case of clinical trial related injury, to be paid by the Sponsor or his representative whosoever had obtained permission from the Licensing Authority as defined under Rule 21(b) for conducting the clinical trial.

(D) In case of clinical trial related injury, the Licensing Authority, shall decide the quantum of compensation to be paid by the Sponsor or his representative whosoever had obtained permission from the Licensing Authority for conducting the clinical trial and shall pass orders as deemed necessary within [1][one hundred and fifty days of the occurrence of the adverse event].

(c) The sponsor or his representative, whosoever had obtained permission from the Licensing Authority for conducting the clinical trial shall pay the compensation in case of clinical trial related injury or death as per the order of the Licensing Authority as defined under Rule 21(b) within thirty days of the receipt of such order.]

---

1. Subs. by G.S.R. 889(E), dt. 12.12.2014.