SECOND SCHEDULE

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

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

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

(i) chemical and pharmaceutical information;

(ii) animal pharmacology data;

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

(b) general pharmacological actions;

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

(iii) animal toxicology data;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(1.1) Systemic toxicity studies,-

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(i) A test for gene mutation in bacteria.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Haematological parameters			
Haemoglobin	Total Red Blood Cell count	Haematocrit	Reticulocyte

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

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

* Organs marked with an asterisk should be weighed.

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

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

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

clinical toxicity studies listed below.

For Phase I Clinical Trials:

Systemic Toxicity studies:-

(I) Single dose toxicitystudies

(II) Dose Ranging Studies

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

Male fertility study:

In-vitro genotoxicity tests, -

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

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

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

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

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

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

In-vivo genotoxicity tests.

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

age are going to be involved).

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

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

Reproductive or developmental toxicity studies

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

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

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

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

Application of Good Laboratory Practices (GLP) -

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

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

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

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

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

1.2 General pharmacological actions,-

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Data should be provided for

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

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

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

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

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

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

Stability testing of new drug substances and formulations:

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

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

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

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

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

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

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

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

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

TABLE 1

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

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

2. Chemical and pharmaceutical information

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

2.2. Physicochemical data.-

(a) Chemical name and Structure

Empirical formula

Molecular weight

(b) Physical properties

Description

Solubility

Rotation

Partition coefficient

Dissociation constant.

2.3. Analytical data

Elemental analysis

Mass spectrum

NMR spectra

IR spectra

UV spectra

Polymorphic identification.

2.4. Complete monograph specification including

Identification

Identity or quantification of impurities

Enantiomeric purity

Assay.

2.5. Validations

Assay method

Impurity estimation method

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

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

Final release specification

Reference standard characterization

Material safety data sheet.

2.7. Data on formulation

(i) Dosage form

(ii) Composition

(iii) Master manufacturing formula

(iv) Details of the formulation (including inactive ingredients)

(v) In process quality control check

(vi) Finished product specification

(vii) Excipient compatibility study

(viii) Validation of the analytical method

(ix) Comparative evaluation with international brand or approved Indian brands, if applicable.

(x) Pack presentation

(xi) Dissolution assay

(xii) Impurities

(xiii) Content uniformity pH

(xiv) Force degradation study

(xv) Stability evaluation in market intended pack at proposed storage conditions

(xvi) Packing specifications

(xvii) Process validation

When the application is for clinical trials only, the international non-proprietary name (INN) or generic name, drug category, dosage form and data supporting stability in the intended container-closure system for the duration of the clinical trial (information covered in item numbers 2.1, 2.3, 2.6, 2.7) are required.

3. Animal pharmacology (for details refer clause 3 of this Schedule)

3.1. Summary

3.2. Specific pharmacological actions

3.3. General pharmacological actions

3.4. Follow-up and supplemental safety pharmacology studies

3.5. Pharmacokinetics: absorption, distribution; metabolism; excretion

4. Animal toxicology (for details refer clause 2 of this Schedule)

4.1. General aspects

4.2. Systemic toxicity studies

4.3. Male fertility study

4.4. Female reproduction and developmental toxicity studies

4.5. Local toxicity

4.6. Allergenicity or Hypersensitivity

4.7. Genotoxicity

4.8. Carcinogenicity

Note: Where the data on animal toxicity as per the specifications of clause 2has been submitted and the same has been considered by the regulatory authority of the country which had earlier approved the drug, the animal toxicity studies shall not be required to be conducted in India except in cases where there are specific concerns recorded in writing.

5. Human or Clinical pharmacology (Phase I)

5.1. Summary

5.2. Specific Pharmacological effects

5.3. General Pharmacological effects

5.4. Pharmacokinetics, absorption, distribution, metabolism, excretion

5.5. Pharmacodynamics / early measurement of drug activity

6. Therapeutic exploratory trials (Phase II)

6.1. Summary

6.2. Study report as given in Table 6 of Third Schedule

7. Therapeutic confirmatory trials (Phase III)

7.1. Summary

7.2. Individual study reports with listing of sites and investigators.

8. Special studies

8.1. Summary

8.2. Bio-availability or Bio-equivalence.

8.3. Other studies e.g. geriatrics, paediatrics, pregnant or nursing women

9. Regulatory status in other countries

9.1. Countries where the drug is

(a) Marketed

(b) Approved

(c) Approved as Investigational New Drug (IND)

(d) Withdrawn, if any, with reasons

9.2. Restrictions on use, if any, in countries where marketed/approved

9.3. Free sale certificate or certificate of analysis, as appropriate.

10. Prescribing information

10.1. Proposed full prescribing information
10.2. Drafts of labels and cartons

11. Samples and Testing protocol/s

11.1. Samples of pure drug substance and finished product (an equivalent of 50 clinical doses, or more number of clinical doses if prescribed by the Central Licencing Authority), with testing protocols, full impurity profile and release specifications.

12. New chemical entity and Global clinical trial:

12.1Assessment of risk versus benefit to the patients
12.2Innovation vis-à-vis existing therapeutic option
12.3 Unmet medical need in the country.

13. Copy of license to manufacture any drug for sale granted by State Licencing Authority (in case the application is for manufacture for sale of new drug)

Note: (1) All items may not be applicable to all drugs. For explanation, refer text of this First Schedule, Second Schedule and Third Schedule.

(2) For requirements of data to be submitted with application for clinical trials refer text of the First Schedule, Second Schedule and Third Schedule.

TABLE 2
DATA REQUIRED TO BE SUBMITTED BY AN APPLICANT FOR GRANT OF PERMISSION TO IMPORT OR MANUFACTURE A NEW DRUG

ALREADY APPROVED IN THE COUNTRY

1. Introduction

A brief description of the drug and the therapeutic class

2. Chemical and pharmaceutical information

2.1 Chemical name, code name or number, if any; non-proprietary or generic name, if any, structure; physico-chemical properties

2.2 Dosage form and its composition

2.3 Test specifications

(a) active ingredients

(b) inactive ingredients

2.4 Tests for identification of the active ingredients and method of its assay

2.5 Specifications of finished product

2.6 Outline of the method of manufacture of active ingredient and finished product

2.7 Stability data

3. Marketing information

3.1 Proposed package insert or promotional literature

3.2 Draft specimen of the label and carton

4. Special studies conducted with approval of Central Licencing Authority

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

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

TABLE 3

DATA REQUIRED TO BE SUBMITTED BY AN APPLICANT FOR CONDUCT OF CLINICAL TRIAL OF AN APPROVED NEW DRUG WITH NEW CLAIMS, NAMELY, NEW INDICATION OR NEW DOSAGE FORM OR NEW ROUTE OF ADMINISTRATION OR NEW STRENGTH OR TO IMPORT OR MANUFACTURE SUCH NEW DRUG FOR SALE OR DISTRIBUTION

1. Number and date of permission or license already granted for the approved new drug.
2. Therapeutic justification for new claim- new indication or modified dosage form/new route of administration

Chemical and Pharmaceutical information

3.1 Chemical name, code name or number, if any; non-proprietary or generic name, if any, structure; physico-chemical properties

3.2 Dosage form and its composition

3.3 Test specifications

(a) active ingredients

(b) inactive ingredients

3.4 Tests for identification of the active ingredients and method of its assay

3.5 Specifications of finished product

3.6 Outline of the method of manufacture of active ingredient and finished product

3.7 Stability data

4. Therapeutic justification for new claim or modified dosage form
5. Animal pharmacological and toxicological data as referred in clause 1, clause 2 and clause 3 of this Schedule.
6. Clinical trial data as referred in clause 1 of this Schedule.
7. Regulatory status in other countries
8. Marketing information:

8.1 Proposed package insert or promotional literature

8.2 Draft specimen of the label and carton

TABLE 4

DATA TO BE SUBMITTED ALONG WITH APPLICATION TO CONDUCT CLINICAL TRIAL OR IMPORT OR MANUFACTURE OF A PHYTOPHARMACEUTICAL DRUG IN THE COUNTRY

PART – A

1. Data to be submitted by the applicant:

1.1.A brief description or summary of the phyto pharmaceutical drug giving the botanical name of the plant (including vernacular or scriptural name, wherever applicable), formulation and route of administration, dosages, therapeutic class for which it is indicated and the claims to be made for the phytopharmaceutical product.

1.2.Published literature including information on plant or product or phytopharmaceutical drug, as a traditional medicine or as an ethno medicine and provide reference to books and other documents, regarding composition, process prescribed, dose or method of usage, proportion of the active ingredients in such traditional preparations per dose or per day's consumption and uses.

1.3.Information on any contraindications, side effects mentioned in traditional medicine or ethno medicine literature or reports on current usage of the formulation.

1.4.Published scientific reports in respect of safety and pharmacological studies relevant for the phytopharmaceutical drug intended to be marketed,-

(a) where the process and usages are similar or same to the product known in traditional medicine or ethno medicine; and

(b) where process or usage is different from that known in traditional medicine or ethno medicine.

1.5.Information on any contraindications, side effects mentioned or reported in any of the studies, information on side effects and adverse reactions reported during current usage of the phytopharmaceutical in the last three years, wherever applicable.

1.6.Present usage of the phytopharmaceutical drug - to establish history of usages, provide details of the product, manufacturer, quantum sold, extent of exposure on human population and number of years for which the product is being sold.

2. Human or clinical pharmacology information:

2.1.Published scientific reports in respect of pharmacological studies including human studies or clinical studies or epidemiological studies, relevant for the phytopharmaceutical drug intended to be marketed,-

(a) where the process and usages are similar or same to the product known in traditional medicine or ethno medicine; and

(b) where process or usage is different from that known in traditional medicine or ethno medicine.

2.2. Pharmacodynamic information (if available).

2.3.Monographs, if any, published on the plant or product or extract or phytopharmaceutical. (Copies of all publications, along with English translation to be attached.)

PART -B

DATA GENERATED BY APPLICANT

3. Identification, authentication and source of plant used for extraction and fractionation:

3.1 Taxonomical identity of the plant used as a source of the phytopharmaceutical drug giving botanical name of genus, species and family, followed by the authority citation (taxonomist's name who named the species), the variety or the cultivar (if any) needs to be mentioned.

3.2 Morphological and anatomical description giving diagnostic features and a photograph of the plant or plant part for further confirmation of identity and authenticity. (Furnish certificate of confirmation of botanical identity by a qualified taxonomist).

3.3 Natural habitat and geographical distribution of the plant and also mention whether the part of the plant used is renewable or destructive and the source whether cultivated or wild.

3.4 Season or time of collection.

3.5 Source of the plant including its geographical location and season or time of collection.

3.6 A statement indicating whether the species is any of the following, namely:-

(a) determined to be endangered or threatened under the Endangered Species Act or the Convention on International Trade in Endangered species (CITES) of wild Fauna and Flora;

(b) entitled to special protection under the Biological Diversity Act, 2002 (18 of 2003);

(c) any known genotypic, chemotypic and ecotypic variability of species.

3.7. A list of grower or supplier (including names and addresses) and information on the following items for each grower or supplier, if available or identified already, including information of primary processing, namely: -

(a) harvest location;

(b) growth conditions;

(c) stage of plant growth at harvest;

(d) harvesting time;

(e) collection, washing, drying and storage conditions;

(f) handling, garbling and transportation;

(g) grinding, pulverising of the plant material; and

(h) sieving for getting uniform particle size of powdered plant material.

3.8. Quality specifications, namely:-

(a) foreign matter;

(b) total ash;

(c) acid insoluble ash;

(d) pesticide residue;

(e) heavy metal contamination;

(f) microbialload;

(g) chromatographic finger print profile with phytochemical reference marker;

(h) assay for bio-active or phytochemical compounds; and

(i) chromatographic fingerprint of a sample as per test method given under quality control of the phytopharmaceutical drug (photo documentation).

3.9 An undertaking to supply specimen sample of plant duly labelled and photocopy of the certificate of identity confirmation issued by a qualified taxonomist along with drawings or photographs of the diagnostic morphological and histological features of the botanical raw material used for the confirmation of authenticity.

4. Process for extraction and subsequent fractionation and purification:

4.1. Quality specifications and test methods for starting material.

4.2. Steps involved in processing.

(a) details of solvent used, extractive values, solvent residue tests or limits,

physico-chemical tests, microbial loads, heavy metal contaminants, chromatographic finger print profile with phytochemical reference markers, assay for active constituents or characteristic markers, if active constituents are not known;

(b) characterisation of final purified fraction;

(c) data on bio-active constituent of final purified fraction;

(d) information on any excipients or diluents or stabiliser or preservative used, if any.

4.3. Details of packaging of the purified and characterised final product, storage conditions and labelling.

5. Formulation of phytopharmaceutical drug applied for:

5.1. Details of the composition, proportion of the final purified fraction with defined markers of phytopharmaceutical drug per unit dose, name and proportions of all excipients, stabilisers and any other agent used and packaging materials.

5.2. Test for identification for the phytopharmaceutical drug.

5.3.Quality specifications for active and inactive phytopharmaceutical chromatographic finger print profile with phytochemical reference marker and assay of active constituent or characteristic chemical marker.

6. Manufacturing process of formulation:

6.1.The outline of the method of manufacture of the dosage form, along with environmental controls, in-process quality control tests and limits for acceptance.

6.2.Details of all packaging materials used, packing steps and description of the final packs.

6.3.Finished product's quality specifications, including tests specific for the dosage form, quality and chromatographic finger print profile with phytochemical reference marker and assay for active constituent or characteristic marker, if active constituents are not known.

7. Stability data:

7.1. Stability data of the phytopharmaceutical drug described at 4 above, stored at room temperature or 40+/- 2 deg. C and humidity at 75%RH +/-5%RHfor 0, 1, 2, 3 and 6 months.

7.2 Stability data of the phytopharmaceutical drug in dosage form or formulation stored at room temperature or 40 +/- 2 deg. C and humidity at 75%RH +/-5%RH for 0, 1, 2, 3 and 6 months, in the pack intended for marketing.

8. Safety and pharmacological information:

8.1. Data on safety and pharmacological studies to be provided.

8.2. Animal toxicity and safety data:

(a) 28 to 90 days repeat dose oral toxicity on two species of animals;

(b) In-vitro genotoxicity data (Ame's test and Chromosomal aberration test);

(c) dermal toxicity tests for topical use products;

(d) teratogenicity study (only if phytopharmaceutical drug is intended for use during pregnancy).

9. Human studies:

9.1.Clinical trials for phytopharmaceutical drugs to be conducted as per applicable Rules and guidelines for new drugs.

9.2.For all phytopharmaceutical drugs data from phase I (to determine maximum tolerated dose and associated toxicities) and the protocols shall be submitted prior to performing the studies.

9.3.Data of results of dose finding studies performed and the protocols shall be submitted prior to performing the studies:

Provided that in the case of phytopharmaceutical drug already marketed for more than five years or where there is adequate published evidence regarding the safety of the phytopharmaceutical drug, the studies may be abbreviated, modified or relaxed.

10. Confirmatory clinical trials:

10.1. Submit protocols for approval for any specific or special safety and efficacy study proposed specific to the phytopharmaceutical drug.

10.2. Submit proposed protocol for approval for human clinical studies appropriate to generate or validate safety and efficacy data for the phytopharmaceutical dosage form or product as per applicable Rules and guidelines.

10.3. Submit information on how the quality of the formulation would be maintained during the above studies.

11. Regulatory status:

11.1. Status of the phytopharmaceutical drug marketed in any country under any category like functional food or dietary supplement or as Traditional medicine or as an approved drug.

12. Marketing information:

12.1. Details of package insert or patient information sheet of the phytopharmaceutical drug to be marketed.

12.2. Draft of the text for label and carton.

13. Post marketing surveillance(PMS):

13.1. The applicant shall furnish periodic safety update reports every six months for the first two years after approval the drug is granted.

13.2. For subsequent two years the periodic safety update reports need to be submitted annually.

14. Any other relevant information:

Any other relevant information which the applicant considers that it will help in scientific evaluation of the application.

THIRD SCHEDULE

(See rules 8, 10, 11, 25, 35, 42 and 49)

CONDUCT OF CLINICAL TRIAL

1. Conduct of clinical trial.-

(i) Clinical trial shall be conducted in accordance with the provisions of the Act and these Rules and principles of Good Clinical Practice Guidelines.

(ii) Clinical trial on a new drug shall be initiated only after the permission has been granted by the Central Licencing Authority and the approval obtained from the respective ethics committee.

(iii)The Central Licencing Authority shall be informed of the approval of the respective institutional ethics committee in accordance with these rules.