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

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

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

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

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

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

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

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

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

FIRST SCHEDULE

(*See rules 19 and 31*)

GENERAL PRINCIPLES AND PRACTICES FOR CLINICAL TRIAL

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

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

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

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

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

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

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

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

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

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

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

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

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

(iii) duration and exposure in clinical trial subject;

(iv) route of administration.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(v) The paediatric studies should include—

(a) clinical trials,

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

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

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

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

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

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

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

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