DRUG BIO-STUDY RULES, 2011

[22nd January, 2011]

S.R.O. 61(I)/2011, dated 13th January, 2011.- The following draft of Drugs (Bio-Study) Rules, 2011, proposed to be made in exercise of the powers conferred by section 43 of the Drugs Act, 1976 (XXXI of 1976), is hereby published, as required by sub-section (3) of the said section, for information of all persons likely to be affected thereby and notice is hereby given that the draft will be taken into consideration by the Federal Government after fifteen days of its publication in the official Gazette.

Any objection or suggestion which may be received from any person in respect of the said draft before the expiry of the said period shall be considered by the Federal Government.

1. Short title and commencement.- (1) These rules may be called the Drugs (Bio-study) Rules, 2011.

(2) They shall come into force at once.

2. Definitions.- In these rules, unless there is anything repugnant in the subject or content,-

(1) **"Bioequivalence"** means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug;

(2) **"Clinical Studies Committee"** The Clinical Studies Committee (CSC) means the Committee constituted under rule 6;

(3) **"Clinical trial"** means any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes. Clinical trials may also be referred to as interventional trials, which include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioral treatments, process-of-care changes, preventive care, etc. This definition includes Phase I to Phase IV trials, namely:-

(i) **Phase I** includes the initial introduction of an Investigational drug into humans. Phase I studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase I, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase II studies. The total number of subjects and patients included in Phase I studies varies with the drug, but is generally in the range of 20 to 80. Phase I studies also include studies of drug metabolism, structure-activity relationships, and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes.

(ii) **Phase II** includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase II studies are typically well controlled, closely monitored, and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

(iii) **Phase III** includes expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase III studies usually include from several hundred to several thousand subjects.

(iv) **Phase IV** (Post Marketing Surveillance Trial) includes the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold or licensed (approved by the Ministry of Health) or treatment is launched, researchers track its safety, seeking more information about a drug or treatment's risks, benefits, and optimal use. Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being no longer sold, or restricted to certain uses. These long–term studies involving large groups of participants continue to see if any unexpected side effects occur in a small percentage of individuals;

(4) **"Contract Research Organization or Clinical Research Organization"** means a person, including a legal person or natural person who assumes, as an independent contractor with the sponsor, one or more of the obligations of a sponsor, e.g., design of a protocol, selection or monitoring of investigations, evaluation of reports, and preparation of materials for Bio-studies;

(5) **"Institutional Review Board"** means any Board, committee, or other group formally designated by an institution to review research studies involving humans as subjects, to approve the initiation of and conduct periodic review of such research studies;

(6) **"Inspection"** means an act of technical audit by the Clinical Studies Committee including an official review of documents, facilities, records, and any other resources that are deemed by the Clinical Studies Committee to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organizations (CRO) facilities, or at other establishments deemed appropriate by the Clinical Studies Committee;

(7) **"Investigational Drug"** means a drug, including placebo that is or may be used in a clinical trial. The term also includes a biological product that is used in vitro for diagnostic purposes;

(8) **"Pharmaceutical alternatives"** means drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates; and

(9) **"Pharmaceutical equivalents"** means drug products in identical dosage forms that contain identical amounts of the identical active drug ingredient, i.e. , the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.

3. Application for license.- (1) An application for the grant of license to conduct clinical trial by a sponsor or clinical research organizations shall be made to the Chairman, Clinical Studies Committee and accompanied by a fee of rupees,

(a) fifty thousand, for each Principal Investigator in clinical trial;
(b) fifteen thousand, for Bioequivalence site approval; and
(c) fifteen thousand, for clinical trial site approval.

(2) Only such sponsors or contract research organizations may make the application which are already registered with the Clinical Studies Committee. The application for registration shall be made on the official letter head of the sponsor or the CRO, as the case may be, with fee of rupees fifty thousands and such further information which the Clinical Studies Committee may require. The registration shall be valid for a period of two years.

(3) Any fee deposited under sub-rule (1) shall, in no case, be refunded.

(4) A sponsor or clinical research organizations who intend to conduct a clinical investigation shall submit an application on Form 1A for approval of clinical trial, in accordance with all the requirements as given in Appendix A.

(5) The investigator shall provide a statement on Form 1B, to the sponsor with the assurance that he will comply with Ministry of Health regulations related to conduct a clinical investigation.

4. Conducting clinical trial.- (1) Clinical trial shall not be conducted except with the prior permission of the Clinical Studies Committee, in accordance with the conditions provided hereunder.-

(i) The Clinical Studies Committee after being satisfied to the effect of scientific justification for such studies shall grant license on Form 2. The approval may be subject to further conditions, if any, as Clinical Studies Committee may deem fit for the safety of the subject.

(ii) If Clinical Studies Committee is not satisfied, it shall reject the application and shall inform the applicant of the reasons for such rejection. If the reasons for rejection are satisfied within a period of thirty days, the application may be reconsidered for issuance of license under the fee already paid.

(iii) The Federal Government may issue Pakistan Good Clinical Practices Guidelines, from time to time, which may lay down criteria for the sites where clinical trials including Bioequivalence studies or such other studies on drugs to which human are subject, shall be conducted and to be observed for conducting such studies provided that where International Conference on Harmonization (ICH) guidelines on the subject are available, the Clinical Studies Committee may require compliance to ICH guidelines as well.

(iv). Provision of the Drugs (Import & Export) Rules, 1976 shall be applicable for the purpose of license to import drugs for clinical trials and permission thereof**.**

5. Labeling Requirements.- The immediate package of an investigational drug intended for human use shall bear a label with the statement "Caution: Drug for investigational use only", prominently. The label or labeling of an investigational drug shall not bear any statement that is false or misleading in any particular and shall not represent that the investigational drug is safe or effective for the purposes for which it is being investigated.

6. Clinical Studies Committee.- (1) The Federal Government shall by notification in the official Gazette constitute a Clinical Studies Committee, consisting of the following member, namely:-

(a) Director General Health, who shall be its ex-officio Chairman.
(b) Drugs Controller (R&D), Ministry of Health, who shall be its ex-officio Vice Chairman.
(c) Deputy Director General (R&D), Ministry of Health.
(d) Chairperson, PMRC.
(e) One Clinical Pharmacist, to be nominated by the Federal Government.
(f) One professor of Pharmacology, to be nominated by the Federal Government.
(g) One representative of Pakistan Pharmaceutical Manufacturer Association and the Pharma Bureau, each having experience and expertise of conducting clinical trials, to be nominated by the Federal Government.
(h) Assistant Drugs Controller (Clinical Trial), Ministry of Health, who shall be its ex-officio secretary.

(2) The members, other than ex-officio members, of the Clinical Studies Committee shall hold office for a period of three years and shall be eligible for renomination for one time.

(3) The quorum to constitute a meeting of the Board shall not be less than five members.

(4) The Clinical Studies Committee shall perform the following functions, namely:-

(a) inspect, by a panel constituted amongst the member of Clinical Studies Committee and any co-opted member under sub rule (1), any site where clinical trials or Bioequivalence or such other studies are proposed to be conducted to satisfy itself of the observance of conditions, guidelines or criteria as notified by the Federal Government under clause (iii) of sub-rule (1) of rule 4 and approve any site for such purpose, provided that such approval shall be valid for a period of two years and renewable for a further term of two years on the payment of prescribed fee and subject to the conditions thereto;

(b) assure the authenticity of scientific justifications for conducting the clinical study;

(c) authorize conduction of such studies and ensure its follow up;

(d) assure that the research team is competent and capable of performing such study, and that they comply with the conditions or guidelines;

(e) assure that volunteers are willing to accept, to undergo such study;

(f) approve the formation of Institutional Review Board; and

(g) evaluate the continuing review report on studies submitted periodically by the Institutional Review Board.

(5) The Clinical Studies Committee may constitute a sub-committee for the performance of any of its functions.

(6) The Clinical Studies Committee may co-opt any subject related expert person for advice on any particular matter under consideration.

(7) The meetings of the Clinical Studies Committee may be held at any time as may be required or on the written request of any of its member; the Chairman may at any time call a meeting within a period of fifteen days if there is any urgent matter for its consideration.

7. Cancellation or suspension of license.- (1) If the licensee does not comply with any of the conditions of the approval or violates any of the provisions of these rules, the Clinical Studies Committee may by an order in writing stating the reasons thereof, cancel a license to conduct the clinical trial, Bioequivalence studies or any such studies, or suspend it for such period as it thinks fit,

(2) The Clinical Studies Committee shall, before canceling or suspending a license under sub-rule (1), conduct an inquiry into the case and provide an opportunity of being heard to the licensee.

(3) When license is cancelled or suspended, an entry to that effect shall be recorded on the license.

8. Withdrawal or Suspension of a clinical investigation of investigational drug.- (1) If at any time, for safety reason or any other ground a clinical trial is withdrawn or suspended anywhere in the world, the sponsor in Pakistan shall forthwith inform Clinical Studies Committee, all participating investigators, and all reviewing Institutional Review Boards, together with the reasons for such withdrawal or suspension.

(2) The Clinical Studies Committee on having an information with regard to the safety of the subject or any other ground, after giving an opportunity of personal hearing to the sponsor, may at it own motion withdrawal or suspend the clinical trial.

(3) The stocks of the investigational drugs shall be returned to the sponsor or otherwise disposed of as the Clinical Studies Committee may allow.

9. Clinical trial under grant in aid.- Where an application for grant in aid is made under the Drugs (Research) Rules 1978, and the applicant submits evidence to this effect, no fee under sub-rule (1) of rule 3 shall be required. However, the study shall be subject to all the conditions, guidelines or criteria as notified by the Federal Government under clause (iii) of sub-rule (1) of rule 4, approval from the Clinical Studies Committee and such further conditions as may be imposed by the Committee of Experts on Drug Research constituted under the Drugs (Research), Rules 1978.

10. Rules not to be derogatory.- These rules shall be in addition to and not in derogation of any other rules framed under the Drugs Act, 1976 (XXXI of 1976).

<table>
<tr><td colspan="2"><u>Form -1A</u>
Application for approval of clinical trial
(Inclusive of information required in Appendix A)
[See rule 3 (4)]</td><td colspan="2">Note: No drug may be shipped or clinical investigation begun until registration for that investigation is in effect</td></tr>
<tr><td>1</td><td>Name of Sponsor/CRO:</td><td colspan="2">2. Date of Submission:</td></tr>
<tr><td>3</td><td>Address.</td><td colspan="2">4. Telephone Number(s) (Include area code)</td></tr>
<tr><td>5</td><td>Name(s) of Drug (Include all available names: Trade, Generic,
Chemical, Code)</td><td colspan="2">6. ID number</td></tr>
<tr><td>7</td><td colspan="3">Indication(s)(covered by this submission)</td></tr>
<tr><td>8</td><td colspan="3">Phase(s) of Clinical Investigation to be conducted:</td></tr>
<tr><td colspan="4">□ PHASE - I □ PHASE-II □ PHASE - III □ OTHER (Specify)----------</td></tr>
<tr><td>9</td><td colspan="3">List numbers of all investigational drug applications, new drug or antibiotic applications, drug master files, and product license application referred to in this application.</td></tr>
<tr><td>10</td><td colspan="2">ID submission should be consecutively numbered. The initial ID should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence should be numbered consecutively in the order in which they are submitted.</td><td>Serial Number</td></tr>
<tr><td>11</td><td colspan="3">This submission contains the followings: (Check all that apply)</td></tr>
<tr><td>A</td><td colspan="2">Initial investigational Drug Application (ID)</td><td></td></tr>
<tr><td>B</td><td colspan="2">Protocol Amendment(s):</td><td></td></tr>
<tr><td></td><td colspan="2">i New Protocol</td><td></td></tr>
<tr><td></td><td colspan="2">ii Change in Protocol</td><td></td></tr>
</table>

	ii New Investigator	
C	Information Amendment(s)	
	i Chemistry / Microbiology	
	ii Pharmacology / Toxicology	
D	Clinical	
E	ID Safety Report(s):	
	i Initial written Report	
	ii Follow up to a written Report	
F	Response to Ministry of Health request for information	
G	Annual Report	
H	General correspondence	
	Request for reinstatement of ID that is withdrawn, inactivated, terminated or discontinued.	
I	Other	

12.	Contents of Application		
	This application contains the following items: (Check all that apply)		
1	Form ID-B		
2	Table of Contents		
3	Introductory statement		
4	General investigational plan		
5	Investigator's brochure		
6	Protocol		
	a	Study protocol(s)	
	b	Investigator data	
	C	Facilities data	
	d	Institutional review board data	
7	Chemistry , manufacturing and control data		
8	Pharmacology and toxicology data		
9	Previous Human experience		
10	Additional information		

13 Is any part of the clinical study to be conducted by a Contract Research Organization?

YES ☐ NO ☐

If yes, will any sponsor obligations be transferred to the Contract Research Organization:

YES ☐ NO ☐

If yes, attach statement containing the following details:

A	Name and address of the Contract Research Organization	
B	Identification of Clinical Study	
C	A Listing of obligations transferred	

14 Name and title of the person responsible for monitoring the conduct and progress of clinical investigations.

15	**Disclaimer**	
I agree that I would not begin clinical investigations until I receive notification by Ministry of Health; I also agree not to begin or continue clinical investigations covered by the Investigational drug if those studies are placed on clinical hold. I agree that and Institutional Review Board (Institutional Review Board) that complies with the requirements set fourth in the Drugs (Bio-Study) rules 2011, will be responsible for initial and continuing review and approval of each of studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.		
16	Name and Signature of the sponsor or sponsor's authorized representative	
18	Address	
19	Telephone Number (Include Area Code)	

For Ministry of Health use only		
Original Fee Challan Amounting to Rs _____ is received and retained for record	Statistical Officer Date:	ID Number Assigned

FORM 1B

[See rule 3 (5)]

FORM 1-B **RSEARCH AND DEVELOPMENT** **MINISTRY OF HEALTH** **STATEMENT OF INVESTIGATOR** **(Inclusive of information required in Appendix A)**	NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed statement of Investigator.
1. Name and address of investigator:	
2.Education, Training, and Experience that qualify the investigator as an expert in the clinical investigation of the drug for the use under investigation. One of the following is attached. ☐ Curriculum Vitae ☐ Other Statement of Qualifications	
3. Name and address of any medical school, hospital, or other research facility (Clinical site) where the	

clinical investigation will be conducted.

4. Name and address of any clinical laboratory facilities to be used in the study.

5. Name and address of the institutional review board that is responsible for review and approval of the study.

6. Names of the sub investigators (e.g. research fellows, residents, associates) who will be assisting the investigator in the conduct of the investigation(s).

7. Name and code number, if any, of the protocol(s) in the Investigational drug (ID) for the study to be conducted by the investigator.

8. Attach the following clinical protocol information:

☐ For Phase I investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.
☐ For Phase II or III investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

9. Commitments:

- I agree to conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the Sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- I agree to personally conduct or supervise the described investigation.
- I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and i will ensure that the requirements relating to obtaining informed consent and institutional Review board, review approval are in accordance to The Drugs (Bio-study) Rules, 2011.
- I agree to report to the sponsor adverse events that occur in the course of the investigation.
- I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- I agree to maintain adequate and accurate records in accordance with conditions/guidelines and the Drugs (Bio-study) Rules, 2011 and to make those records available for inspection in accordance with conditions/guidelines.
- I will ensure that an institutional Review board that complies with the requirements of conditions/guidelines will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the institutional Review board all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without institutional Review board approval, except where necessary to eliminate apparent immediate hazards (conditions/guidelines) to human subjects.
- I agree to comply with all requirements regarding the obligations of clinical investigators and all other pertinent requirements in accordance to conditions/guidelines.

INSTRUCTIONS FOR COMPLETING FORM 1-B
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as in column 2.
3. Attach protocol outline as in column 8.
4. Sign and date below.
5. Forward the completed form and attachments to the sponsor. The sponsor will incorporate this information along with other technical date into an Investigational drug application (Form 1-A).

INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE MINISTRY OF HEALTH.

10. Signature of Investigator

11. Date

Annexure
(UNDERTAKING BY THE INVESTIGATOR)

(i) I have reviewed the clinical protocol and agree that it contains all the necessary information to conduct the study. I will not begin the study until all necessary Institutional Review Board and regulatory approvals have been obtained.

(ii) I agree to conduct the study in accordance with the current protocol. I will not implement any deviation from or changes of the protocol without agreement by the Sponsor and prior review and documented approval or favorable opinion from the Institutional Review Board of

the amendment, except where necessary to eliminate an immediate hazard to the trial Subjects or when the changes involved are only logistical or administrative in nature.

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

(iv) I agree to inform all Subjects that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent and Institutional Review Board review and approval specified in the guidelines are met.

(v) I agree to report to the Sponsor all adverse experiences that occur in the course of the investigation in accordance with the regulatory and guidelines.

(vi) I have read and understood the information in the Investigator's brochure, including the potential risks and side effects of the drug.

(vii) I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are suitably qualified and experienced and they have been informed about their obligations in meeting their commitments in the trial.

(viii) I agree to maintain adequate and accurate records and to make those records available for audit and inspection by the Sponsor, Institutional Review Board, Licensing Authority or their authorized representatives, in accordance with regulatory and guidelines provisions. I will fully cooperate with any study related audit conducted by regulatory officials or authorized representatives of the Sponsor.

(ix) I agree to promptly report to the Institutional Review Board all changes in the clinical trial activities and all unanticipated problems involving risks to human Subjects or others.

(x) I agree to inform all unexpected serious adverse events to the Sponsor as well as the Ethics Committee within seven days of their occurrence.

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

(xii) I agree to comply with all other requirements, guidelines and statutory obligations as applicable to clinical Investigators participating in clinical trials

2. Signature of Investigator with Date

Appendix-A

[See rule 3 (4)]

A. <u>Application for approval of clinical trial.</u>

(1). A sponsor who intends to conduct a clinical investigation subject to this part shall submit an "Application for approval of clinical trial" including, in the following order:

(2). Cover sheet (Form 1A and Form 1B). A cover sheet for the application containing the following:

(a) The name, address, and telephone number of the sponsor, the date of the application, and the name of the investigational new drug.
(b) Identification of the phase or phases of the clinical investigation to be conducted.
(c) A commitment not to begin clinical investigations until an Investigational drug covering the investigations is in effect.
(d) A commitment that an Institutional Review Board that complies with the requirements set forth in guidelines will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation and that the investigator will report to the institutional Review board proposed changes in the research activity in accordance with the requirements of conditions or guidelines.
(e) A commitment to conduct the investigation in accordance with the Drugs (Bio-study) Rules, 2011.
(f) The name and title of the person responsible for monitoring the conduct and progress of the clinical investigations.
(g) The name and title of the person responsible under for review and evaluation of information relevant to the safety of the drug.
(h) If a sponsor has transferred any obligations for the conduct of any clinical study to a contract research organization, a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred. If all obligations governing the conduct of the study have been transferred, a general statement of this transfer--in lieu of a listing of the specific obligations transferred--may be submitted.
(i) The signature of the sponsor or the sponsor's authorized representative. If the person signing the application does not reside or have a place of business within the Pakistan, the ID is required to contain the name and address of, and be countersigned by, an attorney, agent, or other authorized official who resides or maintains a place of business within the Pakistan.

(3). A table of contents.

B <u>Introductory statement and general investigational plan.</u>

(a) A brief introductory statement giving the name of the drug and all active ingredients, the drug's pharmacological class, the structural formula of the drug if applicable, the formulation of the dosage form to be used, the route of administration, and the broad objectives and planned duration of the proposed clinical investigation.

(b) A brief summary of previous human experience with the drug, with reference to other investigational new drug's (ID) if pertinent, and to investigational or marketing experience in other countries that may be relevant to the safety of the proposed clinical investigation.

(c) If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country where the drug was withdrawn and the reasons for the withdrawal.

(d) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following:

(i) The rationale for the drug or the research study;

(ii) the indication to be studied;

(iii) the general approach to be followed in evaluating the drug;

(iv) the kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate);

(v) the estimated number of patients to be given the drug in those studies; and

(vi) Any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

C. <u>Investigator's brochure. A copy of the investigator's brochure, containing the following information:</u>

(i) A brief description of the drug substance and the formulation, including the structural formula, if known.

(ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.

(iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.

(iv) A summary of information relating to safety and effectiveness in humans obtained from prior clinical studies. (Reprints of published articles on such studies may be appended when useful.)

(v) A description of possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs, and of precautions or special monitoring to be done as part of the investigational use of the drug.

D. <u>Protocols.</u>

(i) In general, protocols for Phase I studies may be less detailed and more flexible than protocols for Phase II and III studies. Phase I protocols should be directed primarily at providing an outline of the investigation--an estimate of the number of patients to be involved, a description of safety exclusions, and a description of the dosing plan including duration, dose, or method to be used in determining dose--and should specify in detail only those elements of the study that are critical to safety, such as necessary monitoring of vital signs and blood chemistries. Modifications of the experimental design of Phase I studies that do not affect critical safety assessments are required to be reported to Ministry of Health.

(ii) In Phases II and III, detailed protocols describing all aspects of the study should be submitted. A protocol for a Phase II or III investigation should be designed in such a way that, if the sponsor anticipates that some deviation from the study design may become necessary as the investigation progresses, alternatives or contingencies to provide for such deviation are built into the protocols at the outset. For example, a protocol for a controlled short-term study might include a plan for an early crossover of non responders to an alternative therapy.

(iii) A protocol is required to contain the following, with the specific elements and detail of the protocol reflecting the above distinctions depending on the phase of study:

(a) A statement of the objectives and purpose of the study.

(b) The name and address and a statement of the qualifications (curriculum vitae or other statement of qualifications) of each investigator, and the name of each sub investigator (e.g., research fellow, resident) working under the supervision of the investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.

(c) The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.

(d) A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.

(e) The method for determining the dose to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

(f) A description of the observations and measurements to be made to fulfill the objectives of the study.

(g) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

E. <u>Chemistry, manufacturing, and control information.</u>

(i) Under this heading describing the composition, manufacture, and control of the drug substance and the drug product. Although in each phase of the investigation sufficient information is required to be submitted to assure the proper identification, quality, purity, and strength of the investigational drug, the amount of information needed to make that assurance will vary with the phase of the investigation, the proposed duration of the investigation, the dosage form, and the amount of information otherwise available. Ministry of Health recognizes that modifications to the method of preparation of the new drug substance and dosage form and changes in the dosage form itself are likely as the investigation progresses. Therefore, the emphasis in an initial Phase I submission should generally be placed on the identification and control of the raw materials and the new drug substance. Final specifications for the drug substance and drug product are not expected until the end of the investigational process.

(ii) It should be emphasized that the amount of information to be submitted depends upon the scope of the proposed clinical investigation. For example, although stability data are required in all phases of the Investigational drug (ID) to demonstrate that the new drug

substance and drug product are within acceptable chemical and physical limits for the planned duration of the proposed clinical investigation, if very short-term tests are proposed, the supporting stability data can be correspondingly limited.

(iii) As drug development proceeds and as the scale or production is changed from the pilot-scale production appropriate for the limited initial clinical investigations to the larger-scale production needed for expanded clinical trials, the sponsor should submit information amendments to supplement the initial information submitted on the chemistry, manufacturing, and control processes with information appropriate to the expanded scope of the investigation.

(iv) Reflecting the distinctions described in this paragraph, and based on the phase to be studied, the submission is required to contain the followings:

(a) *Drug substance*.- A description of the drug substance, including its physical, chemical, or biological characteristics; the name and address of its manufacturer; the general method of preparation of the drug substance; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug substance; and information sufficient to support stability of the drug substance during the toxicological studies and the planned clinical studies.

(b) *Drug product:* A list of all components, which may include reasonable alternatives for inactive compounds, used in the manufacture of the investigational drug product, including both those components intended to appear in the drug product and those which may not appear but which are used in the manufacturing process, and, where applicable, the quantitative composition of the investigational drug product, including any reasonable variations that may be expected during the investigational stage; the name and address of the drug product manufacturer; a brief general description of the manufacturing and packaging procedure as appropriate for the product; the acceptable limits and analytical methods used to assure the identity, strength, quality, and purity of the drug product; and information sufficient to assure the product's stability during the planned clinical studies.

(c) A brief general description of the composition, manufacture, and control of any placebo used in a controlled clinical trial.

(d) *Labeling:* A copy of all labels and labeling to be provided to each investigator.

F. Pharmacology and toxicology information. Adequate information about pharmacological and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded, that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required vary with the duration and nature of the proposed clinical investigations. Guidance documents are available from Ministry of Health that describes ways in which these requirements may be met. Such information is required to include the identification and qualifications of the individuals who evaluated the results of such studies and concluded that it is reasonably safe to begin the proposed investigations and a statement of where the investigations were conducted and where the records are available for inspection. As drug development proceeds, the sponsor is required to submit informational amendments, as appropriate, with additional information pertinent to safety.

(i) *Pharmacology and drug disposition.-* A section describing the pharmacological effects and mechanism of action of the drug in animals, and information on the absorption, distribution, metabolism, and excretion of the drug, if known.

(ii) *Toxicology.-* *(a)* An integrated summary of the toxicological effects of the drug in animals and in vitro. Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, sub acute, and chronic toxicity tests; tests of the drug's effects on reproduction and the developing fetus; any special toxicity test related to the drug's particular mode of administration or conditions of use (e.g., inhalation, dermal, or ocular toxicology); and any in vitro studies intended to evaluate drug toxicity.

(iii) For each toxicology study that is intended primarily to support the safety of the proposed clinical investigation, a full tabulation of data suitable for detailed review.

(iv) For each non clinical laboratory study, a statement that the study was conducted in compliance with the good laboratory practice or, if the study was not conducted in compliance with those regulations, a brief statement of the reason for the noncompliance.

G. Previous human experience with the investigational drug. A summary of previous human experience known to the applicant, if any, with the investigational drug. The information is required to include the following:

(i) If the investigational drug has been investigated or marketed previously, either in the Pakistan or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation's rationale. If the drug has been the subject of controlled trials, detailed information on such trials that is relevant to an assessment of the drug's effectiveness for the proposed investigational use(s) should also be provided. Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug's effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.

(ii) If the drug is a combination of drugs previously investigated or marketed, the information required under sub-clause (i) of clause (i) of heading 'J' shall be provided for each active drug component. However, if any component in such combination is subject to an approved marketing application or is otherwise lawfully marketed in Pakistan, the sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component-component interaction).

(iii) If the drug has been marketed outside Pakistan, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness.

H. <u>Additional information.-</u> In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as follows:

(i) <u>Drug dependence and abuse potential.-</u> If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.

(ii) <u>Radioactive drugs.-</u> If the drug is a radioactive drug, sufficient data from animal or human studies to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase I studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

(iii) <u>Pediatric studies.-</u> Plans for assessing pediatric safety and effectiveness.

(iv) Other information**.-** A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.

I. Relevant information: If requested by Ministry of Health, any other relevant information needed for review of the application.

(i) *Information previously submitted***.-** The sponsor ordinarily is not required to resubmit information previously submitted, but may incorporate the information by reference. A reference to information submitted previously must identify the file by name, reference number, volume, and page number where the information can be found. A reference to information submitted by a person other than the sponsor is required to contain a written statement that authorizes the reference and that is signed by the person who submitted the information.

(ii) *Material in a foreign language*.- The sponsor shall submit an accurate and complete English translation of each part of the Investigational drug (ID) that is not in English. The sponsor shall also submit a copy of each original literature publication for which an English translation is submitted.

(iii)*Number of copies*.- The sponsor shall submit an original and two copies of all submissions to the Investigational drug (ID) file, including the original submission and all amendments and reports.

(iv)*Numbering of Investigational drug submissions***.-** Each submission relating to an Investigational drug (ID) is required to be numbered serially using a single, three-digit serial number. The initial Investigational drug (ID) is required to be numbered 000; each subsequent submission (e.g., amendment, report, or correspondence) is required to be numbered chronologically in sequence.

J. Protocol Amendment(s): Once an Investigational drug and clinical trial is in effect, a sponsor shall amend it as needed to ensure that the clinical investigations are conducted according to protocols included in the application. This section sets forth the provisions under which new protocols may be submitted and changes in previously submitted protocols may be made.

(a) **New protocol**. Whenever a sponsor intends to conduct a study that is not covered by a protocol already contained in the Investigational drug (ID), the sponsor shall submit to

Ministry of Health a protocol amendment containing the protocol for the study. Such study may begin provided two conditions are met:

(i) the sponsor has submitted the protocol to Ministry of Health for its review; and

(ii) the protocol has been approved by the Institutional Review Board with responsibility for review and approval of the study in accordance with the requirements of the Drugs (Bio-study) Rules, 2011. The sponsor may comply with these two conditions in either order.

(b) **Changes in a protocol.** (i) A sponsor shall submit a protocol amendment describing any change in a Phase I protocol that significantly affects the safety of subjects or any change in a Phase II or III protocols that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of changes requiring an amendment under this paragraph include:

a) Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.

b) Any significant change in the design of a protocol (such as the addition or dropping of a control group).

c) The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

(ii) A protocol change under sub-clause (i) may be made provided two conditions are met:

a. the sponsor has submitted the change to Ministry of Health for its review; and

b. the change has been approved by the Institutional Review Board with responsibility for review and approval of the study. The sponsor may comply with these two conditions in either order.

(iii) Notwithstanding anything contained in sub-clause (ii), a protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided Ministry of Health is subsequently notified by protocol amendment and the reviewing Institutional Review Board is notified.

(c) New investigator. A sponsor shall submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol, except that a protocol amendment is not required when a licensed practitioner is added in the case of a treatment protocol. Once the investigator is added to the study, the investigational drug may be shipped to the investigator and the investigator may begin participating in the study. The sponsor shall notify Ministry of Health of the new investigator within 30 days of the investigator being added.

(d) Content and format. A protocol amendment is required to be prominently identified as such (*i.e.*, "Protocol Amendment: New Protocol", "Protocol Amendment: Change in Protocol", or "Protocol Amendment: New Investigator"), and to contain the following:

(i) In the case of a new protocol, a copy of the new protocol and a brief description of the most clinically significant differences between it and previous protocols.

(ii) In the case of a change in protocol, a brief description of the change and reference (date and number) to the submission that contained the protocol.

(iii) In the case of a new investigator, the investigator's name, the qualifications to conduct the investigation, reference to the previously submitted protocol, and all additional information about the investigator's study as is required under sub-clause (b) of clause (iii) of heading ‘D’.

(iv) Reference, if necessary, to specific technical information in the Investigational drug (ID) or in a concurrently submitted information amendment to the Investigational drug (ID) that the sponsor relies on to support any clinically significant change in the new or amended protocol. If the reference is made to supporting information already in the Investigational drug (ID), the sponsor shall identify by name, reference number, volume, and page number the location of the information.

(v) If the sponsor desires Ministry of Health to comment on the submission, a request for such comment and the specific questions Ministry of Health’s response should address.

(e) ***When submitted***.- A sponsor shall submit a protocol amendment for a new protocol or a change in protocol before its implementation. Protocol amendments to add a new investigator or to provide additional information about investigators may be grouped and submitted at 30-day intervals. When several submissions of new protocols or protocol

changes are anticipated during a short period, the sponsor is encouraged, to the extent feasible, to include these all in a single submission.

(f) ***Requirement for information amendment***.- A sponsor shall report in information amendment essential information on the Investigational drug (ID) that is not within the scope of a protocol amendment, Investigational drug (ID) safety reports, or annual report. Examples of information requiring an information amendment include:

(a) new toxicology, chemistry, or other technical information; or
(b) a report regarding the discontinuance of a clinical investigation.

(g). ***Content and format of an information amendment***. An information amendment is required to bear prominent identification of its contents (e.g., "Information Amendment: Chemistry, Manufacturing, and Control", "Information Amendment: Pharmacology-Toxicology", "Information Amendment: Clinical"), and to contain the following:

(i) A statement of the nature and purpose of the amendment.
(ii) An organized submission of the data in a format appropriate for scientific review.
(iii) If the sponsor desires Ministry of Health to comment on an information amendment, a request for such comment.

(h) ***When submitted.*** Information amendments to the ID should be submitted as necessary but, to the extent feasible, not more than every 30 days.

(i) **Review and report of safety information**. The sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the agency by the sponsor.

(i) The sponsor shall notify Ministry of Health and all participating investigators in a written Investigational drug (ID) safety report of.-
   a. Any adverse experience associated with the use of the drug that is both serious and unexpected; or

b. Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. Each written notification may be submitted to Ministry of Health or in a narrative format and shall bear prominent identification of its contents, *i.e.*, "Investigational drug (ID) Safety Report." If Ministry of Health determines that additional data are needed, the agency may require further data to be submitted.

(ii) In each written Investigational drug (ID) safety report, the sponsor shall identify all safety reports previously filed with the Investigational drug (ID) concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports.

(iii) ***Reporting format or frequency***.- Ministry of Health may request a sponsor to submit Investigational drug (ID) safety reports in a format or at a frequency different than that required under this paragraph. The sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the Director General (Health) or Drugs Controller (Research and Development) which is responsible for review of the ID.

(iv) ***Disclaimer***.- A safety report or other information submitted by a sponsor under this part (and any release by Ministry of Health of that report or information) does not necessarily reflect a conclusion by the sponsor or Ministry of Health that the report or information constitutes an admission that the drug caused or contributed to an adverse experience. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the drug caused or contributed to an adverse experience.

(j) Progress Report.- A sponsor shall within 60 days of the anniversary date that the Investigational drug (ID) went into effect, submit a brief report of the progress of the investigation that includes.-

(i) ***Individual study information***.- A brief summary of the status of each study in progress and each study completed during the previous year. The summary is required to include the following information for each study:

(a) The title of the study (with any appropriate study identifiers such as protocol number), its purpose, a brief statement identifying the patient population, and a statement as to whether the study is completed.

(b) The total number of subjects initially planned for inclusion in the study; the number entered into the study to date, tabulated by age group, gender, and race; the number whose participation in the study was completed as planned; and the number who dropped out of the study for any reason.

(c) If the study has been completed, or if interim results are known, a brief description of any available study results.

(ii) ***Summary information.-***. Information obtained during the previous year's clinical and non clinical investigations, including:

(a) A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

(b) A summary of all Investigational drugs (ID) safety reports submitted during the past year.

(c) A list of subjects who died during participation in the investigation, with the cause of death for each subject.

(d) A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

(e) A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug's actions, including, for example, information about dose response, information from controlled trials, and information about bioavailability.

(f) A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

(g) A summary of any significant manufacturing or microbiological changes made during the past year.

(iii) A description of the general investigational plan for the coming year to replace that submitted one year earlier.

(iv) If the investigator brochure has been revised, a description of the revision and a copy of the new brochure.

(v) A description of any significant Phase I protocol modifications made during the previous year and not previously reported to the Investigational drug (ID) in a protocol amendment.

(vi) A brief summary of significant foreign marketing developments with the drug during the past year, such as approval of marketing in any country or withdrawal or suspension from marketing in any country.

(vii) If desired by the sponsor, a log of any outstanding business with respect to the Investigational drug (ID) for which the sponsor requests or expects a reply, comment, or meeting.

Form-2
[See rule 4(2)]

LICENSE TO CONDUCT THE CLINICAL TRAIL

No. of License:	Dated:
M/S……. is/are hereby licensed to conduct the clinical trial as detailed below at site …….. or in such other place as the licensing authority may from time to time authorize.	
1. TITLE OF TRIAL	
2. STUDY PHASE OF TRIAL	
3. MEDICINE	
Chemical name	
Non proprietary name	
Trade name	
Indication	
Manufacturer	
4. APPLICANT DETAILS Name Designation	
5. PRINCIPAL INVESTIGATOR (S):	
a) Name b) Position c) Institute d) Site	
6. No. of patients to be enrolled	
7. Maximum duration of trial	
8. Further conditions, if any:	
Licensing Authority:	
Date:	
File No:	