8.3 Packaging information

8.4 Storage and handing instructions

9. Patient Counselling Information

10. Details of manufacturer

11. Details of permission or licence number with date

12. Date of revision

FOURTH SCHEDULE

(See rules 33, 45, 48, 49 and 52)

REQUIREMENTS AND GUIDELINES FOR CONDUCT OF BIOAVAILABILITY AND BIOEQUIVALENCE STUDY OF NEW DRUGS OR INVESTIGATIONAL NEW DRUGS

1. General Principles: (1) Bioavailability or Bioequivalence focus on the release of an active drug from its dosage form and subsequent absorption into the systemic circulation. Bioavailability or Bioequivalence study of a pharmaceutical formulation is one of the components to ensure efficacy and safety of pharmaceutical product.

(2) Bioavailability can be generally documented by a systemic exposure profile obtained by measuring drug or metabolite concentration in the systemic circulation overtime.

(3) Bioequivalence study is conducted to ensure therapeutic equivalence between two pharmaceutically equivalent test product and a reference product.

(4) Bioavailability or Bioequivalence study is conducted to ensure therapeutic equivalence between an approved new drug formulation and reference product for subsequent applicant.

(5) Bioavailability or Bioequivalence study is also conducted to ensure therapeutic equivalence at any phase of clinical trial of a new chemical entity for establishing bioequivalence between two products of the chemical entity, which is important for certain pharmaceutical formulation or manufacturing changes occurring during the drug development stages.

(6) For drugs approved elsewhere in the world and absorbed systemically, bioequivalence with the reference formulation should be carried out wherever applicable. These studies should be conducted under the labelled conditions of administration. Data on the extent of systemic absorption may be required for formulations other than those designed for systemic absorption.

(7) Evaluation of the effect of food on absorption following oral administration should be carried out. Data from dissolution studies should also be submitted for all solid oral dosage forms.

(8) Dissolution and bioavailability data submitted with the new drug application must provide information that assures bioequivalence or establishes bioavailability and dosage correlations between the formulations sought to be marketed and those used for clinical trials during clinical development of the product.

(9) All bioavailability and bioequivalence studies should be conducted according to the Guidelines for Bioavailability and Bioequivalence studies issued by Central Drugs Standard Control Organisation, Ministry of Health and Family Welfare.

(10) Bioavailability and bioequivalence studies of a new drug or investigational new drug shall be conducted in a bioavailability and bioequivalence study centre registered under rule 47 after obtaining permission from the Central Licencing Authority.

2. Bioavailability and bioequivalence study centre:

2.1 The Bioavailability and bioequivalence study centre shall have following facilities for conducting bioavailability and bioequivalence study of any new drug or investigational new drug:

(2.1.1) Legal Identity: The organization, conducting the bioavailability or bioequivalence studies, or the parent organization to which it belongs, must be a legally constituted body with appropriate statutory registrations.

(2.1.2) Impartiality, confidentiality, independence and integrity: The organization shall:

(a) have managerial staff with the authority and the resources needed to discharge their duties.

(b) have arrangements to ensure that its personnel are free from any commercial, financial and other pressures which might adversely affect the quality of their work.

(c) be organised in such a way that confidence in its independence of judgment and integrity is maintained at all times.

(d) have documented policies and procedures, where relevant, to ensure the protection of its sponsors' confidential information and proprietary rights.

(e) not engage in any activity that may jeopardize the trust in its independence of judgment and integrity

(f) have documented policies and procedures for protection of rights, safety and well -being of study subject in consistent with the Provisions of the Drugs and Cosmetics Act and these Rules and Good Clinical Practices Guidelines

(g) have documented policies and procedures for scientific integrity including procedures dealing with and reporting possible scientific misconduct.

(2.1.3) Organisation and management: The study centre must include the following:

(a) An Investigator who has the overall responsibility to provide protection for safety of the study subject. The Investigator(s) should possess appropriate medical qualifications and relevant experience for conducting pharmacokinetic studies.

(b) The site should have facilities and identified adequately qualified and trained personnel to perform the following functions:

(i) Clinical Pharmacological Unit (CPU) management

(ii) Analytical laboratory management

(iii) Data handling and interpretation

(iv) Documentation and report preparation

(v) Quality assurance of all operations in the centre

(2.1.4) Documented Standard Operating Procedures: (1) The center shall establish and maintain a quality system appropriate to the type, range and volume of its activities. All operations at the site must be conducted as per the authorised and documented standard operating procedures.

(2) These documented procedures should be available to the respective personnel for ready reference. The procedures covered must include those that ensure compliance with all aspects of provision of the Act and these rules, good clinical practices guidelines and good laboratory practice guidelines.

(3) A partial list of procedures for which documented standard operating procedures should be available includes:

(a) maintenance of working standards (pure substances) and respective documentation;

(b) withdrawal, storage and handling of biological samples;

(c) maintenance, calibration and validation of instruments;

(d) managing medical as well as non-medical emergency situations;

(e) handling of biological fluids;

(f) managing laboratory hazards;

(g) disposal procedures for clinical samples and laboratory wastes;

(h) documentation of clinical pharmacology unit observations, volunteer data and analytical data;

(i) obtaining informed consent from volunteers;

(j) volunteer screening and recruitment and management of ineligible volunteers;

(k) volunteer recycling (using the same volunteer for more than one study;

(l) randomization code management;

(m) study subject management at the site (including check-in and check-out procedures);

(n) recording and reporting protocol deviations;

(o) recording, reporting and managing scientific misconduct;

(p) monitoring and quality assurance.

(4) Wherever possible, disposable (sterile, wherever applicable) medical devices must be used for making subject interventions.

(5) If services of a laboratory or a facility other than those available at the site (whether with in India or outside the country) are to be availed – its or their names, address and specific services to be used should be documented.

2.1.5) Clinical Pharmacological Unit

(1) It must have adequate space and facilities to house at least 16 volunteers. Adequate area must be provided for dining and recreation of volunteers, separate from their sleeping area.

(2) Additional space and facilities should also be provided for the following:

(a) Office and administrative functions.

(b) Sample collection and storage.

(c) Control sample storage.

(d) Wet chemical laboratory.

(e) Instrumental Laboratory.

(f) Library.

(g) Documentation archival room.

(h) Facility for washing, cleaning and Toilets.

(i) Microbiological laboratory (Optional).

(j) Radio Immuno-Assay room (optional).

3. Maintenance of Records: All records of in *vivo* or in *vitro* tests conducted on any batch of a new drug product to assure that the product meets a bioequivalence requirement shall be maintained by the Sponsor for at least five years after the completion of any study or for at least two years after the expiration date of the batch of the new drug product whichever is later.

4. Retention of Samples: (1) All samples of test and reference drug products used in bioavailability or bioequivalence study should be retained by the organisation carrying out the bioavailability or bioequivalence study for a period of five years after the conduct of the study or one year after the expiry of the drug, whichever is later.

(2) The study sponsor or drug manufacturer should provide to the testing facility batches of the test and reference drug products in such a manner that the reserve samples can be selected randomly.

(3) This is to ensure that the samples are in fact representative of the batches provided by the study sponsor or drug manufacturer and that they are retained in their original containers. Each reserve sample should consist of a quantity sufficient to carry out twice all the in-vitro and in- vivo tests required during bioavailability or bioequivalence study.

(4) The reserve sample should be stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorised personnel.

TABLE 1

DOCUMENT REQUIRED FOR REGISTRATION OF BIOAVAILABILITY AND BIOEQUIVALENCE CENTRE

(1) Name and address of the organization to be registered along with its telephone no., fax no. and email address.

(2) Document regarding legal identity of the centre

(3) Name and address of the proprietors or partners or directors.

(4) An organogram of the centre including brief Curriculum Vitae of Key personnel (Refer para 2.1.3 of this Schedule)

(5) Documents to ensure Impartiality, confidentiality, independence and integrity of the centre**.** Refer para 2.1.2 of this Schedule.

(6) List of equipment in the firm.

(7) List of staff in firm.

(8) List of Standard Operating Procedures for various activities (refer 2.1.4 of this Schedule).

(9) Layout of facility.

(10) Details of Ethics Committee including its registration number.

(11) Facilities for maintenance of records.

(12) Details of Retention of samples.

(13) All major tie ups for ancillary services like ambulance, hospital etc.

TABLE 2
DATA AND INFORMATION REQUIRED FOR GRANT OF PERMISSION TO CONDUCT BIOAVAILABILITY AND BIOEQUIVALENCE STUDY OF A NEW DRUG OR INVESTIGATIONAL NEW DRUG

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

2. Chemical and pharmaceutical information, Animal pharmacological and toxicological data, Clinical trial data - As per Second Schedule.

3. Published reports of Pharmacokinetic and Pharmacodynamics studies carried out in healthy subjects or patients demonstrating safety and tolerability of the molecule.

4. Regulatory status in other countries: Countries where the drug is,-

(a) Marketed.

(b) Approved.

(c) Approved as Investigational New Drug.

(d) Withdrawn, if any, with reasons.

Restrictions on use, if any, in countries where marketed or approved

Free sale certificate or certificate of analysis, as appropriate.

5. Prescribing information of the new drug in case the drug is approved for marketing in the country or other country.

6. Undertaking by the Investigator in original duly signed on a company letterhead as per Table 4 of the Third Schedule.

7. Copy of registration certificate issued by Central Licencing Authority.

8. Sponsor's Authorisation letter duly signed by the Authorised Signatory on company letterhead.

9. The study protocols, informed consent form or patient information sheet along with audio-visual recording system as per requirements of Second Schedule

10. Copy of approval of protocol from the Ethics committee, if available. Copy of registration of the Ethics Committee under rule 8 from the Central Licencing Authority.

11. The study synopsis.

12. Undertaking letter from the sponsor stating that complete medical management in accordance with rule 40 and an undertaking letter from the sponsor stating that compensation in case of study relate injury or death shall be provided in accordance with rule 39.

13. Certificate of Analysis (COA) of representative batches (both Test and Reference formulations) to be used in the BE study along with dissolution profile in case Oral Solid dosage forms.

14. For multiple dose BE study adequate supporting safety data and Pharamcokinetics or Pharmacodynamics should be submitted covering the duration of period for which the study has to be conducted. For all injectable, the sub-acute toxicity should be submitted on the Test product of the sponsor, studied in at least two species for minimum 14 days. If regulatory guidance is available provide a copy of the same.

15. For conducting Bio-Equivalence studies with reference to Cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances and radioactive substances in Healthy Human subjects a Scientific justification with special emphasis on safety of subjects with a proper risk mitigation strategy should be submitted. If regulatory guidance is available provide a copy of the same.

16. For conducting Bio-Equivalence studies with reference to cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances and radioactive substances in Patients a scientific justification with special emphasis on Safety with a proper Risk Mitigation Strategy should be submitted.

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

TABLE 3

DATA AND INFORMATION REQUIRED FOR GRANT OF PERMISSION TO CONDUCT BIOAVAILABILITY AND BIOEQUIVALENCE STUDY OF A NEW DRUG ALREADY APPROVED IN THECOUNTRY

1. Introduction: A brief description of the drug and the therapeutic class to which it belongs.
2. Chemical and pharmaceutical information **-** As per Table 2 of Second Schedule
3. Published reports of Pharmacokinetic and Pharmacodynamics studies carried out in healthy subjects or patients demonstrating safety and tolerability of the molecule.
4. Prescribing information
5. Undertaking by the Investigator in original duly signed on a company letterhead as per Table 4 of Third Schedule.
6. Copy of registration certificate issued by Central Licencing Authority.
7. Sponsor's authorisation letter duly signed by the Authorised Signatory on company letterhead.
8. The study protocols, Informed Consent Form or Patient Information Sheet along with audio-visual recording system as per requirements of Second Schedule.
9. Copy of approval of protocol from the Ethics Committee, if available.
10. Copy of registration of the Ethics Committee under rule 8 from the Central Licencing Authority.
11. The study synopsis.
12. Undertaking letter from the sponsor stating that complete medical management in accordance with rule 40 and an undertaking letter from the sponsor stating that compensation in case of study relate injury or death shall be provided in accordance with rule 39.
13. Certificate of Analysis (COA) of representative batches (both Test and Reference formulations) to be used in the Bio-Equivalence study along with dissolution profile in case Oral Solid dosage forms.
14. For multiple dose BE study adequate supporting safety data and Pharmacokinetics or Pharmacodynamics should be submitted covering the duration of period for which the study has to be conducted.
15. For all Injectable, the sub-acute toxicity should be submitted on the Test product of the sponsor, studied in at least two species for minimum 14 days. If regulatory guidance is available provide a copy of the same.
16. For conducting Bio-Equivalence studies with reference to Cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances and radioactive substances in healthy human subjects a Scientific justification with special emphasis on Safety of subjects with a proper risk mitigation strategy should be submitted. If regulatory guidance is available provide a copy of the same.
17. For conducting Bio-Equivalence studies with reference to cytotoxic drugs, Hormonal preparations, Narcotic and Psychotropic substances and radioactive substances in Patients a scientific justification with special emphasis on Safety with a proper risk mitigation strategy should be submitted.