Available online at www.jcpronline.in

Journal of Current Pharma Research 4 (4), 2014, 1302-1308.

Journal of Current Pharma Research

http://www.jcpronline.in

Review Article

Regulatory Consideration for BA/BE Studies in Indian Scenario.

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Abstract

The term bioequivalence used to describe the equivalence of one brand or dosage form of a drug or supplement to that of reference brand .this equivalence is mastered during *in-vivo* testing in human subjects. To manufacture and market the new drug in India bioequivalence study and phase III studies need to be carried out locally. The purpose is primarily to generate evidence efficacy and safety of drug in Indian population. This review update resent changes in regulatory aspects of BA/BE studies. The changes are means for easy transparent and standardized operation in Indian scenario by CDSCO.

Keywords: Bioequivalence, Study designs, Subjects, regulatory aspects.

Introduction

The term “bioavailability” refers to the extent to which a drug/nutrient reaches its site of action or a biological fluid (such as blood) that has access to site of action. The Relative bioavailability is assessed using a reference product and “absolute bioavailability” is determined using the Intravenous as 100%. The term “bioequivalence” refers to pharmaceutically equivalent drug products where the rates/extents of bioavailability of the actives are not significantly different under suitable test conditions. In other words, this is a comparison of two or more products with respect to their bioavailability. Bioequivalence is a term in pharmacokinetics used to judge the expected in vivo biological equivalence of two proprietary preparations of a drug. If two products are said to be bioequivalent it means that they would be expected to be same for all senses and purposes. According to regulations applicable in the European Economic Area two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailability after administration in the same molar dose is similar to such a degree that their effects, with respect to both efficacy and safety, will be essentially same. Bio-equivalent means that one brand or dosage form of a drug or supplement is equivalent to a reference brand or dosage form of the same drug or supplement in terms of various bioavailability parameters measured via in vivo testing in human subjects. Bio-equivalence cannot be declared on the basis of animal studies only. Bio-equivalence of human drugs must be determined in humans via established measures of bioavailability. By the same token animal drugs must be tested for bio-equivalence in the animal species for which the drug in intended. Once bio-equivalence has been established via bioavailability testing in a statistically significant manner subsequent batches of the same product are deemed bio-equivalent based on in-vitro measures such as drug dissolution. The statutory definition of BA and BE, expressed in rate and extent of absorption of the active moiety or ingredient to the site of action, emphasizes the use of pharmacokinetic measures to indicate release of the drug substance from the drug product with absorption into the systemic circulation. The basic steps and requirements at any BA/BE studies vary as per the regulatory guidelines from countries however the

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someone steps involved in BA/BE studies one described bellow in figure.

Basic Steps and Requirements for BA/BE Studies

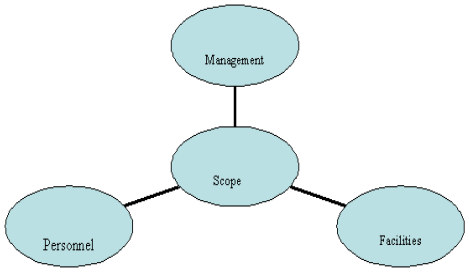
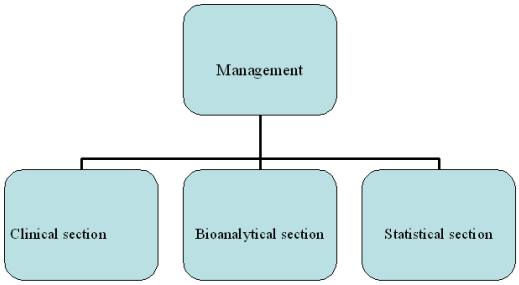


Figure No.1

The management team is important key to manage the successful study in bioequivalence so these are four main basic areas to consider the manage all aspect of study conduction in BA/BE.



Clinical section

The clinical section is part of bioequivalence to conduct systematic study on human to generate the data for safety and efficacy of drug for approval from regulatory.

Bioanalytical section

The bioanalytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice (GLP) and cGMP. Bioanalytical methods used to determine the active moiety and/or its metabolic product(s) in plasma, serum, blood or urine, or any other suitable matrix, should be well characterized, and fully validated and documented to yield reliable results that can be satisfactorily interpreted. The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of an analyte(s) in a specific biological matrix. Validation should, therefore, address the following characteristics of the assay.

a) Stability of stock solutions.
b) Stability of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage.
c) Specificity.
d) Accuracy.
e) Precision.
f) Limits of detection and quantification.
g) Response function.
i) Robustness and ruggedness.

A calibration curve should be generated for each analyte in each analytical run, and it should be used to calculate the concentration of the analyte in the unknown samples in the run. A number of separately prepared Quality Control samples should be analyzed with processed test samples at intervals based on the total number of samples. All procedures should be performed according to pre-established Standard Operating Procedures (SOPs).
All relevant procedures and formulae, used to validate the bioanalytical method, should be submitted and discussed. Any modification of the bioanalytical method, before and during analysis of study specimens, may quire adequate revalidation, and all modifications should be reported and the scope of revalidation justified.

Statistical section

Pharmacokinetic & statistical analysis for plasma concentration vs. time profile of the study drug which is performed by the data obtaining from all subjects who completed the study. Pharmacokinetic parameter such as Cmax, AUC_{∞}, AUC_{last}, is calculated by using SAS 9.2. Pharmacokinetic analysis is done using the blood or plasma concentration-time profile. The pharmacokinetic parameters to be measured depend on the type of study whether single dose or multiple-dose study.

Ethics Committee

The basic responsibility of an Independent Ethics Committee is to ensure a competent

review of all ethical aspects of the project proposals received & executes the same, free from any bias & influence that could affect their objectivity. The responsibility of an IEC can be defined as follows:

- To protect the dignity, rights & well being of the potential research participants.
- To ensure that universal ethical values & international scientific standards are expressed in terms of local community values & customs.
- To assist in the development & the education of a research community responsive to local health care requirements.
- One lay person from the community.
- Member Secretary

Regulatory Authorities of Some Countries

There are numbers of regulatory guidelines which prescribe different set of aspects to the ICH guidelines are accepted throughout globule to achieve uniformity in drug information for public benefits the table no.1 enumerate different govt agenises.

Important terminologies In BA/BE studies

1. **Active Pharmaceutical Ingredient (API):** API is a substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active ingredient.
2. **Bioavailability:** Bioavailability refers to the rate and extent of the drug that reaches to systemic circulation.
3. **Bioequivalence:** Bioequivalence is defined as the absence of a significant difference in bioavailability between two pharmaceutically equivalent products under similar conditions of study.
4. **Generic Pharmaceutical Product**: Generic pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent or bioequivalent.
5. **Pharmaceutical Equivalence:** Pharmaceutical products are pharmaceutically equivalent if they contain the same amount of the same API(s) in the same dosage form, if they meet the same or comparable standards and if they are intended to be administered by the same route.

Biopharmaceutics Classification System (BCS)

The BCS is a scientific framework for classifying medicinal substances based on their aqueous solubility and intestinal permeability. According to the BCS, medicinal substances are classified as follows:

Class 1: High solubility – High permeability
Class 2: Low solubility – High permeability
Class 3: High solubility – Low permeability
Class 4: Low solubility – Low permeability

Regulatory Considerations in Bioequivalence Studies

Study design

The study should be considered in such a way that the formulation effect can be distinguished from other effects. Study designs should be well established with proper statistical analysis. If required steady-state study design should be motivated.

To avoid carry-over effects, treatments should be separated by adequate wash-out periods. The sampling schedule should be planned to provide an adequate estimation of C_{max} and AUC.

If a reliable estimate of terminal half-life is necessary, it should be obtained by collecting at least three to four samples. For long half-life drugs (> 24 hours) the study should cover a minimum of 72 hours. Successfully determining the BE of generic drugs to their respective reference drugs depends mostly on design and managing the conduct of study such that the highest quality samples are obtained.

Subjects

The minimum number of subjects should not be less than 12 to meet acceptance criteria. A minimum of 20 subjects is required for modified release oral dosage forms to meet acceptance criteria. The studies should in general be performed with healthy volunteers. Subjects may be selected from either sex.

However, the risk to women of childbearing potential should be considered on an individual basis. Subjects should be between 18 and 55 years of age. Subjects should have a body mass within the normal range of BMI (Body Mass Index).

All subjects participating in the study should be capable of giving informed consent. Subjects should be screened for clinical laboratory tests, medical history and medical examination. Subjects should preferably be non-smokers and without a history of alcohol or drug abuse. If the API under investigation is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy volunteers, it may be necessary to use patients instead, under suitable precautions and supervision. The time of day for ingestion of doses should be specified. The volume of fluid administered at the time of dosing should be constant. In fasted studies the period of fasting prior to dosing should be standardised and supervised. All meals and fluids taken after dosing should also be standardised in regard to composition and time of administration. Subjects should not take other medicines for a suitable period prior to and during, the study. Posture and physical activity of the subject may need to be standardised. Sampling points should be chosen such that the plasma concentration *versus* time profiles can be defined adequately, thereby allowing accurate estimation of relevant parameters.

Statistical Requirements

In the case of API's predominantly excreted by renal route, the use of urine excretion data may be advantageous in determining the extent of drug input. All pharmacodynamics measurements/methods should be validated with respect to specificity, accuracy and reproducibility. The bioanalytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice (GLP) and current Good Manufacturing Practices (cGMP). Test products in an application for a generic product are normally compared with the comparable dosage form. The choice of reference product should be justified by the applicant if outside the WHO reference comparator list. A sufficient number of retention samples of both test and reference products used in the bioequivalence study, should be kept for one year in excess of the accepted shelf-life, or two years after completion of the trial or until approval, whichever is longer, in order to allow re-testing if required by SADC. A complete audit path of procurement, storage, transport and use of both the test and reference products should be recorded. The statistical method for testing relative bioavailability is based upon the 90 % confidence interval for the ratio of the population means (Test/Reference) for the parameters under consideration. Pharmacokinetic parameters derived from measures of concentration should be analysed using ANOVA. In addition to the appropriate 90 % confidence intervals, summary statistics such as geometric and arithmetic means, SD and % RSD, as well as ranges for pharmacokinetic parameters (minimum and maximum), should be provided. The general descending order of first choice of these studies includes pharmacokinetic, pharmacodynamic, clinical and in vitro studies. Pharmacokinetic endpoint studies are most widely preferred to assess BE for drug products, where drug level can be determined in an easily accessible biological fluid (such as plasma, blood, urine) and drug level is correlated with the clinical effect.

Clinical section of the bioequivalence study report

It includes:

a) A statement indicating the independence of the ethics committee.

b) Documented proof of ethical approval of the study.

c) A complete list of the members of the ethics committee, their qualifications and affiliations.

d) Names and affiliations of all investigator(s), the site of the study and the period of its execution.

e) The names and batch numbers of the products being tested.

f) The name and address of the applicant of both the reference and the test products.

g) Expiry date of the reference product and the date of manufacture of the test product used in the study.

h) Assay and dissolution profiles for test and reference products.
i) Certificate of analysis (CoA) of the API.
j) A summary of adverse events of the study.
k) A summary of protocol deviations.
l) Subjects who drop out or are withdrawn from the study.

Analytical section of the bioequivalence report

It includes:
a) The full analytical validation report.
b) All individual subject concentration data.
c) Calibration data.
d) Quality control samples for the entire study.
e) Chromatograms from analytical run.
f) A summary of protocol deviation

Pharmacokinetic and statistical section of the bioequivalence report:

It includes:
1) All individual plasma concentration versus time profiles presented on a linear/linear as well as log/linear scale.
2) The methods and programmes used to derive the pharmacokinetic parameters from the raw data.
3) A detailed ANOVA and/or non-parametric analysis, the point estimates and corresponding confidence intervals for each parameter of interest.
4) Tabulated summaries of pharmacokinetic and statistical data.

Regulatory authorities, regulatory aspects and international efforts in bioequivalence assessment

Due to considerable recognition of the BA/BE concept all over the world, tremendous advancements have been made by the FDA as well as various national, international and supranational regulatory authorities. Pharmaceutical industry and academia are also contributing solely in the area of assessment of BE. The currently available excellent scientific and regulatory guidance is due to the combined efforts of industry, academia and regulatory scientists. Every country now has its own self regulatory authority as well as regulatory guidance for BA/BE studies. In the United States, the FDA approves and grants marketing authorization of generic drugs by applying the regulatory requirements provided in the Code of Federal Regulations.

Assessment of bioequivalence

The estimation of BE of different drug products is based on the basic assumption that two products are equal when the rate and extent of absorption of the test/generic drug does not show a significant difference from the rate and extent of absorption of the reference/brand drug under similar experimental conditions as defined. As per the different regulatory authorities, BE studies are generally classified as:

- Pharmacokinetic endpoint studies.
- Pharmacodynamic endpoint studies.
- Clinical endpoint studies.
- In vitro endpoint studies.

End Point Studies

1. Pharmacodynamic endpoint studies: Pharmacokinetic studies assess systemic exposure but are generally unfortunate to document local delivery BA and BE. BA may be measured and BE may be established, based on a pharmacodynamic study, providing an appropriate pharmacodynamic endpoint is available.
2. In vitro endpoint studies:

A Biopharmaceutics Classification System (BCS) has categorized drug substances as having either high or low solubility or permeability and drug products as exhibiting rapid dissolution.
3. Clinical endpoint studies or comparative clinical trials:

In the absence of pharmacokinetic and pharmacodynamic approaches, adequate and well-controlled clinical trials may be used to establish BA/BE.

The general considerations for the advancement of conducting BA/BE studies:

a) Study design and protocol.
b) Bio analysis.
c) Selection of appropriate analyte(s).
d) BE metrics and data treatment.
e) Statistical approaches and analysis.
f) Acceptance criteria for BE

The resent changes in study protocol are introduced to increase the transparency authentically and accuracy to standard the protocol.

Procedure and draft guidelines on Audio-Visual recording of informed consent Process in Bioequivalence study.

Principle of Privacy and Confidentiality

During the audio-video (AV) recoding of informed consent process, the identity and records of trial subjects are as far as kept confidential; and that no details about identity of said subjects, which would result in disclosure of their identity, are disclosed without valid scientific and legal reasons which may be essential for the purposes of therapeutics or other inventions, without the specific consent in writing of the subject concerned, or someone authorized on their behalf, and after ensuring that the said subject does not suffer from any form of hardship, discrimination or stigmatization as a consequence of having participated in the trial.

The investigator must safeguard the confidentiality of trial data, which might lead to identification of the individual subjects. Data of the individual subjects can be disclosed only in a court of law under the orders of the presiding judge or in some cases may be required to communicate to drug regulatory/ Health authority.

In order to maintain the confidentiality, the videographer should be engaged as part of the study team. Prior to initiation of the study, the investigator should define and allocate the activities of audio-video recording of informed consent process to the respective identified person as videographer. The investigator shall maintain the details of the person to whom he has delegated the duties of audio video recording.

a) Consent of the Subjects for Audio-Video Recording

Prior consent of the subject should be taken for audio-visual recording of informed consent process and the same should be documented by the investigator. Such consent may be taken orally. Only those subjects who give the consent for the AV recording shall be included in the clinical trial.

b) Procedure of Audio-Visual Recording

At the beginning of the video recording process, the investigator will identify the protocol, the subject /LAR/IW and the language understood by the subject / LAR/IW. If the investigator does not know the language of the subject / LAR/ IW a member of the study team who understands the language, would become the interpreter.

In order to indentify the subject / LAR /IW his / her photo ID may be documented. The video camera for the audio-visual recording should be of adequate capability to simultaneously capture the facial details of subject, LAR / Impartial Witness (if any), investigator / authorized person present during the consent process. The audio visual recording should be conducted in a room conductive to recoding of disturbance free audio and video of the consent process. During the videography process, care should be taken not to include unrelated persons / patients at the hospital within the field of vision.

c) Quality of Audio- Visual Recording

The video recording of informed consent may not serve the intended purpose if the quality of recording fails to meet a minimum standard required for the purpose. The video recording should be done using video camera of appropriate resolution and in a room free from any disturbance to ensure that the image is recognizable and the audio is clearly audible.

d) Storage and Archival of Audio-Visual Recordings

Audio visual recording of informed consent process and other related documents should be preserved safely after the completion / termination of the study for at least a period of 5 years if it is not possible to maintain the same permanently

Conclusion

Bioequivalence studies conducted to assess therapeutic equivalence between two drug formulations are generally carried out between an innovator brand formulation and a generic formulation. The assessment of bioequivalence *in vivo* and *in vitro* has taken more and more attention in pharmaceutical companies and biological companies. Before a

new drug is introduced into the market, clinical trials are conducted to test for safety, tolerability and effectiveness. An equivalence approach is generally recommended, which usually relies on a criteria to allow the comparison, a confidence interval for the criterion and a BE limit. The overall objective of BE is to ensure that generic products have efficacy and safety characteristics similar to those of the corresponding reference product. All the official guidelines are strictly followed during BA/BE studies

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Table 1: Regulatory Authorities of Some Country.

Sr. No.	Country	Regulatory Authority
1	India	Central Drugs Standard Control Organization
2	Unites States of America	US Food and Drug Administration
3	Europe	European Medicines Agency
4	Australia	Therapeutic Goods Administration
5	Japan	Pharmaceuticals and Medical Devices Agency
6	Sri Lanka	Ministry of Health
7	Germany	Federal Institute for Drugs and Medical Devices
8	Ireland	Irish Medicines Board
9	Italy	National Institute of Health
10	Spain	Spanish Drug Agency
11	Switzerland	Swiss Agency for Therapeutic Products
12	Brazil	National Health Surveillance Agency