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Bioequivalence studies for pharmaceutical products

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ABSTRACT

This review is the summary of Bioequivalence, Bioavailability and its related parameters. Brief description of Bioavailability and Bioequivalence is explained along with the post approval changes. There is a major role played by Bioavailability and Bioequivalence or the development of a drug for generic products. A bioequivalence study is required for generic products so that the rate and extent of drug can be explained which is clinically trivial. The design and conduct of Bioequivalence studies is explained which includes the selection of subject, number of subjects and dosing pattern. This article reviews the role and studies of Bioavailability and Bioequivalence in pharmaceutics.

Keywords: *bioequivalence; bioavailability; post approval changes; ANDA; NDA; pharmacokinetics.*

1. INTRODUCTION

The globally arranged important data and statistics have been provided by Bioavailability (BA) and Bioequivalence (BE). Through BA and BE, the accessibility of innocuous and effective medication has been confirmed to the patient and consultants. Thus some have systematic exposure measures in which the measures of BA and BE are recurrently articulated such as Maximum Concentration (C_{max}) and Maximum Time (T_{max}). Thus systematic exposure measures are thought that they are associated with the safety and competence results which are narrated in terms of biomarkers or Surrogate end points [1]. So, the information obtained from BA and BE based on all these assumptions has been made to have some realistic and communal health importance for many sectors such as pharmaceutical benefactors, regulatory organization and patients and doctors.

FDA Review: There was some data detected which made national and international exertions to explain and describe Bioavailability and Bioequivalence and also proper ways and methods for their appraisal [2]. The importance of BA and BE was endorsed by a key report issued by the Congressional office of Technology Assessment in the United States. They also specified additional steps to confirm this information to become a part of the development of drug and supervisory procedure, some additional steps are also specified by this [3]. FDA adopted the recommendation of this report and was published in 1977 [4]. BE also had some additional importance for generics drug after the passage of Drug Price Competition and amendments in 1984.

The comparison of systematic exposure outline of dissimilar dosage form and route of administration can be done by Bioavailability study. So, the information obtained from BA along with pharmacokinetic and pharmacodynamics in this perspective can be used to validate the resemblance between 2 dosages forms [5].

Bioavailability: The measurement of the active ingredients plasma concentration or blood concentration can be obtained from systemic exposure profile through which Bioavailability can be described for generally orally consumable drug products. Various useful information's may also be provided by BA from along with systemic exposure as per pharmacokinetic viewpoint. Thus additional information is about distribution, metabolism, elimination of drug, effect of nutrients on the absorption of drug, etc.

Bioequivalence: Bioavailability is a part of Bioequivalence. The performance of Bioequivalence study emphasis on drug product comparatively. The relative bioavailability of two drug products is assessed by Bioequivalence [6]. Even though BA proves to be a benchmark in establishing the product quality. But then too without any comparison, Bioequivalence (BE) is a formal relative test generally between a test product and reference product. Specific criteria have been used for the comparison and pre-ordinated BE limits. Several circumstances have been discussed in which evaluation of BE might be important.

INDs-NDAs: During the period of INDs-NDAs, documentation of BE can prove to be useful to establish links between:

- Formulation used in clinical trials and the drug products which are to be marketed.
- Formulations that are used in clinical and stability studies, if they are different.

In a piece comparison, Test product is the new method or new formulation used in the manufacture and the reference product is the previous formulation or manufacturing method used previously [7]. Sometimes, due to the inadequacy of the number of subjects that taking entry in the Bioequivalence study, Bioequivalence is observed.

NDAs: ANDAs basically establish between generic drug products and the resembling listed drug that is pharmaceutical equivalent.

Post Approval Changes: Information required for the post approval changes are provided as either NDAs or ANDAs on the types of studies of *in vivo* Bioequivalence and *in vitro* dissolution. Thus information was presented in FDA guidance. New guidance has been published on post approval change which was known as

"CMC post approval manufacturing changes [8]. To be documented in Annual Reports". It was required by FDA that changes must be proclaimed regarding approved NDAs or ANDAs. The changes having meager or negligible capacity on affecting the assurity, effectiveness and quality of the product were reported on anannual basis. So as per such situation, Drug product after having changes should be analyzed with the drug product before any change for approved NDAs and for approved ANDAs, the drug product after having changes should be compared with that of the listed reference drug.

Requirement of Bioequivalence for General Products: Many procedures have been established by many countries so that generic pharmaceutical product can be familiarized. So, in this case, the therapeutic equivalence of these generic products must be displayed to a preceding accepted and permitted product so that the consumers can be protected. This therapeutic equivalence is revealed on the basis of bioequivalence demonstration. Bioequivalence i.e., the assessment of pharmacokinetic measurement to determine the disparities in the rate and extent of the absorption of drug that is clinically trivial. The most suitable proof authenticate the equivalence between pharmaceutical products is generally evidenced by Bioequivalence. However the products can be therapeutic as therapeutic equivalent, and not bioequivalent, if the difference in rate of absorption is observed in some cases, the disparity shown in the rate of absorption does not have therapeutic significance.

Bioequivalence Study for Generic Products: The bioequivalence study should be vindicated for those generic products which are proposed to be an alternative for a previously approved product. TGA has adopted the guidelines of European Communities for the testing of his equivalence. Various measures have been provided by these guidelines to evaluate products having systemic action and also for non-oral immediate and modified release product that have systematic actions [9]. Two situations are also specified but this EC guideline does not show the relevance of Bioavailability studies. The first one is for the generic products which are like simple solutions intended to be used only as intravenous administration and gas intended to be used as inhalations. The second one for those generic products intended for local use.

2. DESIGN AND CONDUCT OF BIOEQUIVALENCE STUDY

A number of matters are needed to be taken into consideration before designing the bioequivalence study minimize the irrelevant inconsistency and some factors are also through which quality of relative Bioequivalence might get influenced. To design a satisfactory Bioequivalence study, some additional knowledge also necessary regarding pharmacokinetics, pharmacodynamics and toxicology of drug. Human Research ethics committed authorization is mandatory before the study being conducted [10,11].

- **Study Design:** Balanced crossover design study is used in which thus is an unplanned distribution of subjects in all the sequences, so as to lesser the inconsistency. For example, an incomplete block design may be appropriate to use. So that the study interval can be reduced or the number of drug exposure can be restricted. This takes place when more than two treatments are involved in the study. So, to obtain the same accuracy is this type of experimental design, more numbers of subjects are required [12].
- **Single or Multiple Dozing:** For the assessment of Bioequivalence study, single dose studies are suitable generally. But, some conditions are required in case of multiple-dose studies.
  - Those formulations which are controlled release.
  - When marked or targeted dose dependent exhibited by drug.
  - When the nature of the drug precludes the use of healthy volunteers.

The recommendation of FDA governs that multiple dose studies are used in those cases when a difference is seen in the rate of absorption but not in the extent of absorption. The pharmacokinetics of the drug must be taken into consideration if study of multiple dosing is involved. Through this, the necessary dosing interval can be determined so that steady state condition can be attained.

- **Subject Selection**: Adult and healthy volunteers are generally used to conduct this study, aged between 18-55 years. As both sexes of subjects are involved, the involvements of females are considered for the reproduction toxicity of drug. Some criteria are used to determine the studies i.e. medical history of subject, physical examination is performed and some other significant investigation is done. If smokers are used as

the subject, then it should be clearly mentioned in the report. Along with the smoking time, quantity of cigarettes smoking is also recommended to be monitored [13].

- **Number of Subjects**: The number of subjects is taken in such a way that meaningful results can be obtained. An extremely large number of subjects cannot be accepted for the study. The error variance of the principle parameter which is to be examined determines the number of subjects required in the Bioequivalence study. As per Canadian and European guidelines, the minimum number required is 12 for the BE study. Large number of subject is required in the case where large error variance is seen in drugs [10].

Bioequivalence study of Glucocorticoids: Glucocorticoid is the drug that is more often prescribed by Dermatologists. It has properties like vaso-constructive nature, anti-inflammatory, anti-proliferative, due to which it becomes effective in the treatment of Psoriasis and atopic dermatitis. Glucocorticoid receptor on the site of action for topical glucocorticoids (Tg) which are present in viable epidermis and dermis. To assess the bioavailability/bioequivalence of Tg, several *in vitro* and *in vivo* methods have been inculcated [14].

In vivo:

- Clinical trial
- Vasoconstrictor assay: Tape stripping, Microdialysis

In vitro:

- Release study
- Permeation study

Clinical trials are the only accepted method through which the BA/BE of topically applied drugs can be assessed between generic and prior products. Comparatively small numbers of subjects are required by the pharmacodynamics response studies and also a small amount of formulation is needed to expose the subjects or a short span of time [15]. The vasoconstriction o the skin is produced by the ability of Tg pharmacodynamics response which leads to the whitening of skin. Mckenzie and Stoughton [16,17]

were the first who described "vasoconstriction assay". The BA/BE of corticosteroid formulation has been measure by this vasoconstrictor assay in healthy volunteers [18,19,20].

Bioavailability studies: in the late 1960s, a public issue was originated that was related to Bioavailability-Bioequivalence concept as lesser bioavailability is shown by generic drug product as compared to the drug product fabricated by the manufacturer. Clinical consideration of these types of concern in human and along with this minimal drug quantity can be quantified in biological fluids. Because of this a rigourous research and development were initiated for around a period of three decades. Alongwith this for generic drug product approval, formulation and process were also started. These phases are classified for bioavailability and bioequivalence research and development which are given as follows:

1. Phase I- from early 1970s to 1984
2. Phase II- 1984 to 1992
3. Phase III- since 1992 to 21st Century

3. PHARMACOKINETIC PARAMETERS

The absorption and elimination of drug are often studied with the help of Pharma concentration time curve, after the drug administration. The administrator route of drug is proportional to the absorption rate generally. So as compared to oral administration of drug, the plasma-concentration time curve profile can be studied such as T_{max} (time taken to attain maximum concentration), C_{max} (maximum concentration), AUC (Area under Curve) etc. Among all AUC is one of the primary pharmacokinetic parameter in the study of Bioavailability- Bioequivalence.

Clinical Significant Differences: For the therapeutic equivalence assessment, clinically important differences are useful which are defined in terms of Safety, efficacy and risk ratio. Therapeutic equivalence is considered in terms of Bioequivalence in Bioavailability-Bioequivalence studies. Some data is obtained with the help of evaluation of clinical efficacy, safety and blood concentration through which Clinical trials may relate clinical ultimate points to Bioavailability specifications. However, these Clinical trials went to a rigorous possible phase to verify bioequivalence assumptions. Following mentioned difficulties are carried out with such Clinical trials such as:

1. Healthy subjects rarely went for bioavailability-bioequivalence studies as compared to suffering individual which cannot be well controlled.
2. Suffering individuals are more variegated in a wide array of peculiarities.

It is not necessarily valid that the differences were shown between statically important differences and Clinical differences unquestionably imply with each other in comparing the bioavailability amid drug products shown by Westlake [20].

There are some parameters on which limits for Bioequivalence depend with respect to therapeutic equivalence such as Drug nature, population of patients and Clinical ultimate points which is used to evaluate the therapeutic effect. For this, some equivalence limits was proposed by FDA for Clinical endpoints [21] shown in the Table 1.

Table 1. Equivalence limits for clinical endpoints proposed by FDA.

Rate of Response for the Reference drug (%)	Equivalence Limits (%)
>95	±5
90-95	±10
80-90	±15

4. BIOEQUIVALENCE EVALUATION

There are some integral Bioequivalence assumptions on which the bioequivalence evaluation is based on different drug products:

Two drug products are assumed to be equivalent therapeutically, when the rate and extent of two different drug products are equal to each other through which the absorption of Active drug ingredient takes place and the drug becomes available at the site of drug action.

So, for the evaluation of therapeutic equivalence in terms of Safety and efficacy amid drug products, the Clinical trials are considered to be the surrogates for bioequivalence studies as given by the integral Bioequivalence Assumption. Hence, Pharmaceutical equivalents or Pharmaceutical alternatives are identified by means of equivalence Bioequivalence trials that can be intercommutable showing similar effects. This is why therapeutic equivalents products are considered as Bioequivalent drug products and that can be used in place of each other.

"Prescribability" or "Switchability" is the two terms that are used as the Classification for drug inter-commutability indicated by Hauck and Coworkers [22] and Chow and Coworkers [23]**.** When a Physician prescribes suitable drug of choice to a new suffering patient among the drug product of manufacturer is known as Drug Prescribability. Population Bioequivalence is generally used to assess Drug Prescribability. When the same subject is used in the entire process in which the manufacturer drug product is switched to generic drug product having a steady or constant Concentration of active ingredient then it is known as Drug Sustainability.

Decision Rules: Practically, it is difficult to assess the combination amid significant clinical difference and bioequivalence limits between 1977 and 1992, FDA proposed some decision rules So as to test the Bioequivalence in respect of average bioavailability of precise drugs.

1. The 75/75 Rule: when maximum 75% of the ratio of respective subject falls within limit, then Bioequivalence is asserted.
2. The 80/20 Rule: Bioequivalence is claimed if 20% difference of reference average there is minimum 80% detection power and the test average and reference average is a bit similar with no statistical importance differences.
3. The ±20 Rule: when within the limit of ±20% of reference formulation, test formulation's average bioavailability falls then Bioequivalence is claimed within an assured affirmation.
4. The 80/125 Rule: When within the limit of (80%, 125%) of reference formulation, test formulation's average bioavailability falls then Bioequivalence is claimed within an assured affirmation.

Basic Design Consideration: Following points are used to determine in-vivo bioavailability study that indicates a basic design by FDA such as:

a. Reference materials Nature and Test dosage form.
b. Answers of some scientific questions.
c. Analytical Method's Accessibility.
Consideration of benefit Risk with respect to testing on humans.

5. CONCLUSIONS

It can be concluded from the above review that Bioequivalence study is required to test generic products. This study is done to guard customers against taking inferior drug products. The design and conduct required for Bioequivalence study are explained in the review which includes subject selection, number of subjects, dosing pattern etc. Recommendations of FDA are also provided for drug products in order to establish Bioequivalence and Bioavailability.

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