

Bioequivalence Studies

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1. Introduction

During last four decades there is an increased use of generic drug products in order to lower the healthcare cost. With increased availability and use of generic drug products, healthcare professionals are encountered with a large number of multisource products from which they have to select therapeutically equivalent products. Generic substitution is of concern not only for healthcare professionals but also for pharmaceutical industries, consumers and government officials. Many research papers have pointed out the concern regarding standards for approval of generic products which may not always ensure therapeutic equivalence (Boix-Montanes, 2011; Skelly, 2010; Tothfalusi et al., 2009; Midha et al., 2005; Chen & Lesko, 2001; Chen et al., 2000; Strom, 1987; Lamy, 1986). To alleviate this fear many guidelines/guidance and regulations covering the licensing of generic products have been introduced to ensure that the medicinal products reaching the market have well-established efficacy and safety profile (FDA, 1992, 1996, 2001a, 2001b, 2003, 2011; CDSCO, 2005; SFDA, 2005; Health Canada, 2004; CPMP, 2000; WHO, 1986).

Generally, demonstration of bioequivalence (BE) is the most appropriate method of ensuring therapeutic equivalence between two medicinal products. Bioequivalence studies should be conducted for comparison of medicinal products containing same active substance. Such studies need to be carefully designed to take into account biopharmaceutical, ethical, medical, pharmacokinetic, analytical and statistical considerations. The studies should be aimed to critically assess the possibility of alternate use of these products. In the 2003 United States Food and Drug Administration (FDA) guidance, bioequivalence is defined as:

“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” (FDA, 2003).

Bioequivalence is actually the comparison of the bioavailability of two drug products. In the 2003 United States Food and Drug Administration (FDA) guidance, bioavailability is defined as:

“the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action. For drug products that are not

intended to be absorbed into the blood stream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action" (FDA, 2003).

According to World Health Organization (WHO) guidelines, bioavailability is defined as:

"the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action" (WHO, 1986).

According to the United States Food and Drug Administration (FDA) "pharmaceutical equivalents" are drug products that contain identical active ingredients and are identical in strength or concentration, dosage form, and route of administration (FDA, 2011).

The CPMP (Committee for Proprietary Medicinal Products) guidance on bioavailability and bioequivalence confers the concept of therapeutic equivalence as:

"A medicinal product is therapeutically equivalent with another product if it contains the same active substance or therapeutic moiety and, clinically, shows the same efficacy and safety as that product, whose efficacy and safety has been established. In practice, demonstration of bioequivalence is generally the most appropriate method of substantiating therapeutic equivalence between medicinal products, which are pharmaceutically equivalent or pharmaceutical alternatives, provided they contain excipients generally recognized as not having an influence on safety and efficacy and comply with labeling requirements with respect to excipients. However in some cases where similar extent of absorption but different rates of absorption are observed, the products can still be judged therapeutically equivalent if those differences are not of therapeutic relevance. A clinical study to prove that differences in absorption rate are not therapeutically relevant, will probably be necessary" (CPMP, 2000).

In early 1960's extensive work in pharmacokinetics offered substantial evidence that composition and dosage form of a drug product can affect *in vivo* properties as well as therapeutic effects. These differences have been attributed to the effect of different drug excipients used, variations in manufacturing procedures and the properties of final dosage form on the rate and extent of the drug absorption from its site of administration. The importance of bioavailability came into lime-light after an incidence in Australia where a change in an inactive excipient of phenytoin formulation by the manufacturer resulted in low plasma levels of active drug leading to therapeutic failure and seizures in epileptic patients who were previously well-controlled with the same dose of same drug. Similarly in Europe marked variations in the plasma levels of digoxin were observed with different preparations of the drug resulting in either toxicity or therapeutic failure (Crawford et al., 2006; Welage et al., 2001; Soryal & Richens, 1992; Lindenbaum et al., 1971; Tyrer et al., 1970).

Bioequivalence and bioavailability studies are important during drug development of both new drug products and their generic equivalents. Provision of bioavailability and/or bioequivalence study data is an important element in support of Investigational New Drug Applications (INDs), New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs) and their supplements. The term generic drug product has been defined as "interchangeable multi-source pharmaceutical product". Generic products are the copies of brand-name drugs with same dosage form, strength, route of administration, intended use

and toxicity profile as the original innovator drug. Concern about lowering healthcare costs has resulted in an increase in the use of cheaper generic drug products instead of branded products. The innovator drugs are protected from copying by patents that last for 20 years from the first filing of the new chemical entity. Many people are concerned why generic drugs are often cheaper than the brand-name versions. It is because all the development work and clinical trials on new chemical entity are carried out by innovator to get initial drug approval which is later on reflected in its high price whereas the generic manufacturers only need to submit the bioequivalence data of the generic product to get a product license. The new products need to undergo bioequivalence testing before they are marketed. The difference may exist in absorption reflected in differing bioavailability profile of various brands, production batches or dosage forms of a drug. This can lead to either over- or under-medication if one entity is substituted for the other. The under-medication can lead to therapeutic failure and on the other hand over-medication can lead to toxicity. To avoid such risk it is best to study the bioavailability of all products but practically it is not possible. So each drug and any change in formulation must be considered individually while keeping in mind the real medical need for such studies in order to ensure efficacy and safety of these drugs. Many clinicians while switching or interchanging the different products are concerned with the safety and effectiveness of the new product. This concern is because of the fact that small changes in bioavailability can lead to significant changes in the efficacy or safety of the drug. Bioequivalence studies are designed with this concern in mind and to devise the strategies that minimize the risk to the patient. So when the generic product is pharmaceutically equivalent as well as bioequivalent to the innovator drug, then it is expected to be therapeutically equivalent (Kowalski et al., 2006; Crawford et al., 2006; FDA, 2003; Welage et al., 2001; Vasquez & Min, 1999; Banahan & Kolassa, 1997; Benet & Goyan, 1995; Marzo and Balant, 1995; WHO, 1986).

2. Design and conduct of bioequivalence studies

The basis of a bioequivalence study is the comparison of the drug product to be tested with an appropriate reference product (branded innovator drug). In bioequivalence studies an applicant compares the systemic exposure profile of a test drug to that of a reference drug product. Bioequivalence of two products can be assessed using *in vitro* standards, pharmacokinetic profile, clinical or pharmacodynamic end points. Different approaches for determination of bioequivalence of a drug product are:

- An *in vivo* test in humans in which the concentration of the active ingredient and when appropriate, its active metabolites, in blood, plasma, serum or other suitable biological fluid is measured as a function of time.
- An *in vivo* test in humans in which the urinary excretion of the active ingredient and when appropriate, its active metabolites are measured as a function of time.
- An *in vitro* test that has been correlated with and is predictive of human bioavailability profile or the one acceptable to FDA (e.g. dissolution rate test) that ensures human *in vivo* bioavailability.
- An *in vivo* test in humans in which an appropriate pharmacological effect of the active ingredient and when appropriate, its active metabolites are measured as a function of time if this effect can be measured with adequate accuracy, sensitivity and reproducibility.

- Well-controlled clinical trials that establish the efficacy and safety of the drug product, for purpose of determining bioavailability, or comparative clinical trials, for purpose of demonstrating bioequivalence.
- Any other approach considered adequate by the FDA to measure bioavailability or ascertain bioequivalence.

Bioequivalence for most of oral tablets or capsules is demonstrated *in vivo* by comparing the rate and extent of absorption that is bioavailability of the generic product with that of the innovator product. This is done by measuring the active ingredient concentration in blood, plasma, serum or other biological fluids over a certain period of time for both the generic and innovator products, also called test and reference drugs respectively. By doing so the bioequivalence studies frequently rely on pharmacokinetic measures such as area under the concentration-time curve (AUC) and peak drug concentration (C_{max}) (Niazi, 2007; FDA, 2001a, 2003; Pidgen, 1996; Nation & Sanson, 1994).

2.1 Study design

Many authors have debated whether multi-dose or single-dose studies should be used to assess bioequivalence. Generally single-dose pharmacokinetic studies are recommended for both immediate- and modified-release drug products as they are more sensitive in assessing the active ingredient released from drug into circulation. For assessing bioequivalence of two formulations of a drug, two-sequence, two-period, crossover study is conducted after administration of single dose under fasted conditions. In crossover design the subjects serve as their own controls and they crossover from one treatment to the other. A large variability in drug clearance often exists among the individuals. However the intrasubject variation is usually smaller relative to inter-subjects variability. Parallel studies are appropriate if the drug has extremely long half life, repeated pharmacokinetic profile is difficult to obtain, or residual pharmacodynamic effects are relevant. Furthermore, if carry over effects from one treatment period to another are of concern or if intrasubject variability is high, then replicated design is used. Nonreplicate study designs are usually recommended for bioequivalence studies of most of the orally administered, modified-release and immediate-release dosage forms. Replicate study designs are often recommended for bioequivalence studies of highly variable drug products (intra-subject coefficient of variation $\geq 30\%$), including those that are modified-release, immediate release, and other orally administered drug products. Replicate study designs have several scientific advantages compared to nonreplicate designs. (SFDA, 2005; FDA, 2001a, 2003; Welage et al., 2001; Nation & Sanson, 1994; Steinijs et al., 1992; Metzler, 1989).

2.2 Study subjects

The subjects should be selected with the objective of minimizing variability and permitting detection of difference between the drug products. Therefore, the study is normally carried out with healthy subjects. The study is performed in accordance with the Declaration of Helsinki for biomedical research involving human subjects (WMA Declaration of Helsinki, 2008) and the Guideline for Good Clinical Practice (FDA, 1996). The subjects recruited for bioequivalence studies should be 18 years of age or older and

capable of giving informed consent. Generally adults between 20-40 years should be selected. According to FDA guidance and Canadian and European guidelines a minimum of 12 subjects are recruited for bioequivalence studies. For logistic reasons the total number normally does not exceed 24 subjects. The subjects should be in good health. The subject's health is assessed by medical examination including medical history and laboratory tests. They should be screened for the history of use of medications or drugs of abuse, alcohol intake and smoking. The subjects should not take any medication one week before start of study (CDSCO, 2005; FDA, 2001a, 2003; Marzo & Balant, 1995; Nation & Sanson, 1994; WHO, 1986).

2.3 Drug administration and sampling

A bioequivalence study should be a single dose comparison of test drug with appropriate reference drug product carried out in healthy adults. The drug is administered to the subjects in fasting state, unless some other approach is more suitable for valid scientific reasons. Co-administration of food with oral drugs may either enhance or interfere with drug absorption. Thus, feeding increases the inter- and intra-subject variations in rate and extent of absorption. The sponsor should provide the rationale for conducting bioequivalence study under fed or fasting conditions. The subjects are randomly selected for each group in the study and the sequence of drug administration is randomly assigned to the individuals. In a typical situation of comparing a test formulation (T) with a reference formulation (R), the two-period, two-sequence crossover design is the RT/TR design as shown in table 1. Subjects are randomly allocated to two treatment sequences; in sequence 1, subjects receive the reference drug and test drug in periods 1 and 2 respectively, on the other hand in sequence 2, subjects receive the drug products in reverse order. The administration of each product is followed by a sufficiently long wash out period of time to ensure complete elimination of drug before next administration. A time period of more than 5 half-lives of the drug is considered adequate washout period. In selected cases, it may be necessary for the test and reference products to be compared after multiple-dose administration to determine steady-state levels of the active drug moiety. A multiple-dose study should be crossover in design, unless a parallel or other design is more suitable for valid scientific reasons (Hauschke et al., 2007; Niazi, 2007; FDA, 2003; Makoid et al., 1999).

In fasted state studies an overnight fast of at least 10 hours is recommended. Generally in single dose studies the highest marketed strength is administered. The doses of the test and reference products should be same. The test or reference products are administered with 240 ml of water. Liquids are allowed after one hour and standard meal after 4 hours of drug administration. In all the studies the standardization of study environment, diet, fluid intake and exercise is important (CDSCO, 2005; FDA, 2003; WHO, 1986).

Sequence	Period 1	Washout	Period 2
1	R		T
2	T		R

Table 1. RT/TR Design

Under most of the conditions blood or plasma is collected rather than urine or tissue. Blood samples are drawn at appropriate times to assess the absorption, distribution and elimination phases of the drug. For most of the drugs 12-18 samples are recommended including pre-dose sample from each subject. Generally sampling for a period equal to at least 3 times the terminal half life of the drug is recommended. Other approach is that the duration of sampling should be sufficient to define at least 80% of the total area under the concentration-time curve (AUC). The exact timings for sampling depend on nature and pharmacokinetic profile of individual drug and its dosage form (FDA, 2001a, 2003; Nation & Sanson, 1994; WHO, 1986).

2.4 Bioanalytical methodology

The measurement of drug concentration in collected samples is done through bioanalytical methods. Prior to sample analysis, the selected analytical method is validated in accordance with the recommended guidelines (Niazi, 2007; ICH, 2005; FDA, 2001b). Assay validation involves different steps:

- Quality control samples
- Identification and specificity
- Sensitivity and limit of detection
- Range, linearity and limit of quantitation
- Precision and accuracy
- Analyte and system stability
- Reproducibility

A properly validated assay method is crucial for the acceptance of any pharmacokinetic study. During validation, quality control samples are run in replicates to assess the intra- and inter-day variability during sample analysis.

2.5 Data analysis

Data analysis is carried out:

- By direct observation and measurement
- By simple mathematical calculations
- By use of different softwares

2.5.1 Pharmacokinetic analysis

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 (FDA, 1992).

For single dose bioequivalence study the parameters are:

- Area under the plasma / blood concentration-time curve from time zero to time t (AUC_{0-t}), calculated by trapezoidal rule, where t is the last measurable time point.

- Area under the plasma / blood concentration-time curve from time zero to time infinity ($AUC_{0-\infty}$) where

$$AUC_{0-\infty} = AUC_t + C_t / \lambda_z$$

C_t is the last measurable drug concentration and λ_z is the terminal elimination rate constant calculated according to an appropriate method. The terminal or elimination half life of the drug should also be documented.

- Peak drug concentration (C_{max}) and the time to peak drug concentration (T_{max}), obtained directly from the data without interpolation.

For multiple-dose studies, the parameters measured are:

- Area under the plasma / blood concentration-time curve from time zero to time τ over a dosing interval at steady state ($AUC_{0-\tau}$), where τ is the dosing interval.
- Peak drug concentration (C_{max}) and the time to peak drug concentration (T_{max}), obtained directly from the data without interpolation, after the last dose is administered.
- Drug concentrations at the end of each dosing interval during steady state (C_{min}).
- Average drug concentration at steady state (C_{av}), where $C_{av} = AUC_{0-\tau} / \tau$.
- Degree of fluctuation (DF) at steady state, where $DF = 100\% \times (C_{max} - C_{min}) / C_{av}$.

2.5.2 Statistical analysis

The pharmacokinetic parameters AUC and C_{max} are analyzed statistically to determine if the test and reference products produce comparable values. The FDA's statistical criteria for approval of test or generic drugs requires calculation of a confidence interval (CI) for the ratio between the means of test and reference product's pharmacokinetic variables. The two products are said to be bioequivalent if the 90% CI for the ratio of test to reference formulation falls within the bioequivalence acceptance range of 80-120% for data in original scale and 80-125% for log-transformed data of AUC and C_{max} . This method is equivalent to a testing procedure called two one-sided tests (TOST) procedure, where one test verifies that the bioavailability of the test product is not too low and the other to show that it is not too high as compared to standard reference product. The current practice is to carry out two one-sided tests (TOST) procedure with the null hypothesis (H_0) of non-bioequivalence at 5% level of significance ($\alpha=0.05$). Traditional statistical approach is often designed to test the null hypothesis of equality. If data is sufficiently strong, null hypothesis is rejected and alternate hypothesis (H_1) is accepted. Before 1980s, most of the bioequivalence studies were conducted in this way; researchers tested for differences between drug formulations and if they found none, they concluded them to be bioequivalent (i.e. H_0 = bioequivalence, H_1 = non-bioequivalence). During further studies, many flaws were recognized in this approach. If sample size was large enough, minor differences even not important clinically, were found to be significant, whereas if sample size was small, the potential important differences were neglected. The purpose of bioequivalence (BE) study is generally not to demonstrate a difference but to assess the equivalence of test product to that of reference standard. So the method of difference statistics with null hypothesis of no difference is not applicable to BE studies.

Instead, the equivalence testing with the null hypothesis of a difference or non-bioequivalence is used. According to the FDA this difference is set at $-20 / +25$ percent. In order to verify that $-20 / +25$ percent rule is satisfied, the two one-sided tests are carried out. The rejection of the two one-sided tests null hypotheses at 5% level of significance ($\alpha=0.05$) is equivalent to the inclusion of the 90 percent CI in the acceptance range (Hauschke et al., 2007; Riffenburgh, 2006; Welage et al., 2001; FDA, 1992, 2001a; Pidgen, 1996; Hauck & Anderson, 1992; Schuirmann, 1987).

The statistical analysis ANOVA (analysis of variance) is used to calculate estimates of the error variance. ANOVA should be performed on AUC and C_{max} accounting for the sources of variation which are:

- Sequence (group)
- Subjects in a sequence
- Period (phase)
- Treatment (drug formulation).

The results of ANOVA are calculated at 5% level of significance ($\alpha=0.05$). The sponsor may use untransformed or log-transformed data. The choice should be made with concurrence by the FDA prior to conducting the study. The validity of statistical analysis is improved by log-transforming the raw data prior to analysis (FDA, 1992).

2.6 Presentation and documentation of data

The drug concentration in the biological fluid at each sampling time point for all the subjects should be presented in original form. Pharmacokinetic parameters like C_{max}, C_{min}, T_{max} are directly observed from original data. Pharmacokinetic parameters like AUC_{0-t}, AUC_{0-∞}, AUC_{0-t}, λ_z, t_{1/2} are derived from original data by mathematical calculations or by using different softwares like APO MWPHARM, PK Solutions, PK-fit and WinNonlin PK software. The pharmacokinetic data recommended for submission is:

- Plasma concentrations and time points
- Subject, period, sequence, treatment
- AUC_{0-t}, AUC_{0-∞}, λ_z, t_{1/2}, C_{max} and T_{max}
- AUC_{0-t}, C_{min}, C_{av} and degree of fluctuation are also submitted for multiple-dose studies
- Intersubject, intrasubject, and/or total variability

The mean values and standard deviation (SD) can be calculated by computer programs like Microsoft Excel, SAS, SPSS. The statistical analysis for bioequivalence testing is carried out by using different computer softwares like EquivTest 2.0, Minitab Release 13.1, BioEquiv and DAS 2.0 software. The statistical information recommended to be provided for pharmacokinetic parameters are:

- Geometric mean
- Arithmetic mean
- Ratio of means
- Confidence interval

Bioequivalence parameters can be presented in tabulated form as shown in table 2.

Parameters	Test mean \pm SD	Reference mean \pm SD	Ratio of Geometric means	90 percent confidence interval
AUC _(0-t) (hr.mg/l)				
AUC _(0-∞) (hr.mg/l)				
Cmax (mg/l)				
Tmax (hrs)				

Table 2. Bioequivalence Parameters

3. Waivers of *in vivo* bioequivalence studies

Under certain circumstances, FDA may waive the requirement for *in vivo* bioequivalence studies if drug product meets one of the following criteria:

- When the drug product is a parenteral solution intended solely for administration by injection, and contains the active drug ingredient in the same solvent and concentration as a solution that is subject of an approved full New Drug Application (NDA).
- The drug product is a topically applied preparation intended for local therapeutic effect e.g. ophthalmic/otic solutions or it is administered by inhalation and contains the active drug ingredient in the same dosage form as a drug product that is the subject of an approved full NDA and ANDA.
- The drug product is a solution for application to the skin, an oral solution, elixir, syrup, tincture, a solution for nebulization, a nasal solution, or similar other solubilized form, and contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full NDA or ANDA, and contains no inactive ingredient or other change in formulation from the drug product that is the subject of an approved full NDA and ANDA that may significantly affect absorption of the active drug ingredient or moiety for products that are systemically absorbed, or that may significantly affect systemic or local availability for products intended to act locally.
- The drug product is a solid oral dosage form (other than controlled release or enteric-coated) that has been determined to be effective for at least one indication in a Drug Efficacy Study Implementation (DESI) notice and is not included in the FDA list of drugs for which *in vivo* bioequivalence testing is required.
- The *in vivo* bioavailability or bioequivalence may be self-evident for certain drug products. The FDA may waive the requirement for the submission of evidence obtained by *in vivo* measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug product's *in vivo* bioavailability or bioequivalence may be considered self-evident based on other data in the application.
- For certain drug products, bioavailability or bioequivalence may be demonstrated by evidence obtained *in vitro* in lieu of *in vivo* data. The FDA may waive the requirement of the submission of *in vivo* data if a drug product meets the following criteria:

- The drug product is in the same dosage form, but in the different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has got the approval and certain conditions are met, that the bioavailability of this other drug product has been measured and both meet an appropriate *in vitro* test approved by the FDA; and the applicant submits evidence showing that both products are proportionally similar in their active and inactive ingredients.
- The drug product is shown to meet an *in vitro* test that assures bioavailability, that *in vitro* test has been correlated with *in vivo* data.
- The drug product, for which only an *in vitro* bioequivalence data has been required by FDA for approval.
- The drug product is a reformulated product that is identical, except for a different color, flavor, or preservative, to another drug product for which the same manufacturer has obtained approval and the following conditions are met: the bioavailability of the other product has been measured; and both the drug products meet an appropriate *in vitro* test approved by the FDA.

In above circumstances bioequivalence studies may be waived by the drug regulatory authorities (FDA, 2011, 2000, 2003; Niazi, 2007; CDSCO, 2005; Makoid et al., 1999).

4. Conclusion

Keeping in view the health-care cost, the pharmaceutical companies are manufacturing and marketing cheaper generic drug products. It is vital for the regulatory authorities of every country to ensure the efficacy and safety of these generic formulations. Carefully planned and designed bioequivalence studies are the only way to ensure uniformity in standards of quality, efficacy and safety of pharmaceutical products.

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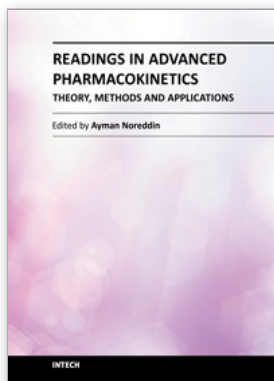
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