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Research

Principle And Guidelines For Be Studies For Approval Of ANDA

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Abstract

The present study was aimed to study the requirements of bioequivalence for the registration of pharmaceutical products. Before going into bioequivalence studies it is essential for the pharmaceutical industry to study the guidelines of bioequivalence for the respective country where the industry wants to market its products and thus enter into generic market. This study reviews the requirements of bioequivalence with study parameters such as study design, fasting or fed state studies, volunteers recruitment, study dose, sampling points, analytical method validation parameters, moieties to be measured in plasma, pharmacokinetic parameters, criteria for bioequivalence, which are needed for the pharmaceutical industry to carry out bioequivalence studies and to file ANDA. Test products and reference products are needed for this study. Test products are usually manufactured by a sponsor and reference products are provided by the government laboratories of the respective countries. Sampling points also vary with respect to the regulatory guidelines of a country.

Keywords: Raphia hookeri, total antioxidant

INTRODUCTION

Bioequivalence studies are special type of studies where two drugs or two sets of formulation of the same drug are compared to show that they have nearly equal bioavailability and PK/PD parameters. These studies are often done for generic drugs or when a formulation of a drug is changed during development.

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).[1-8]

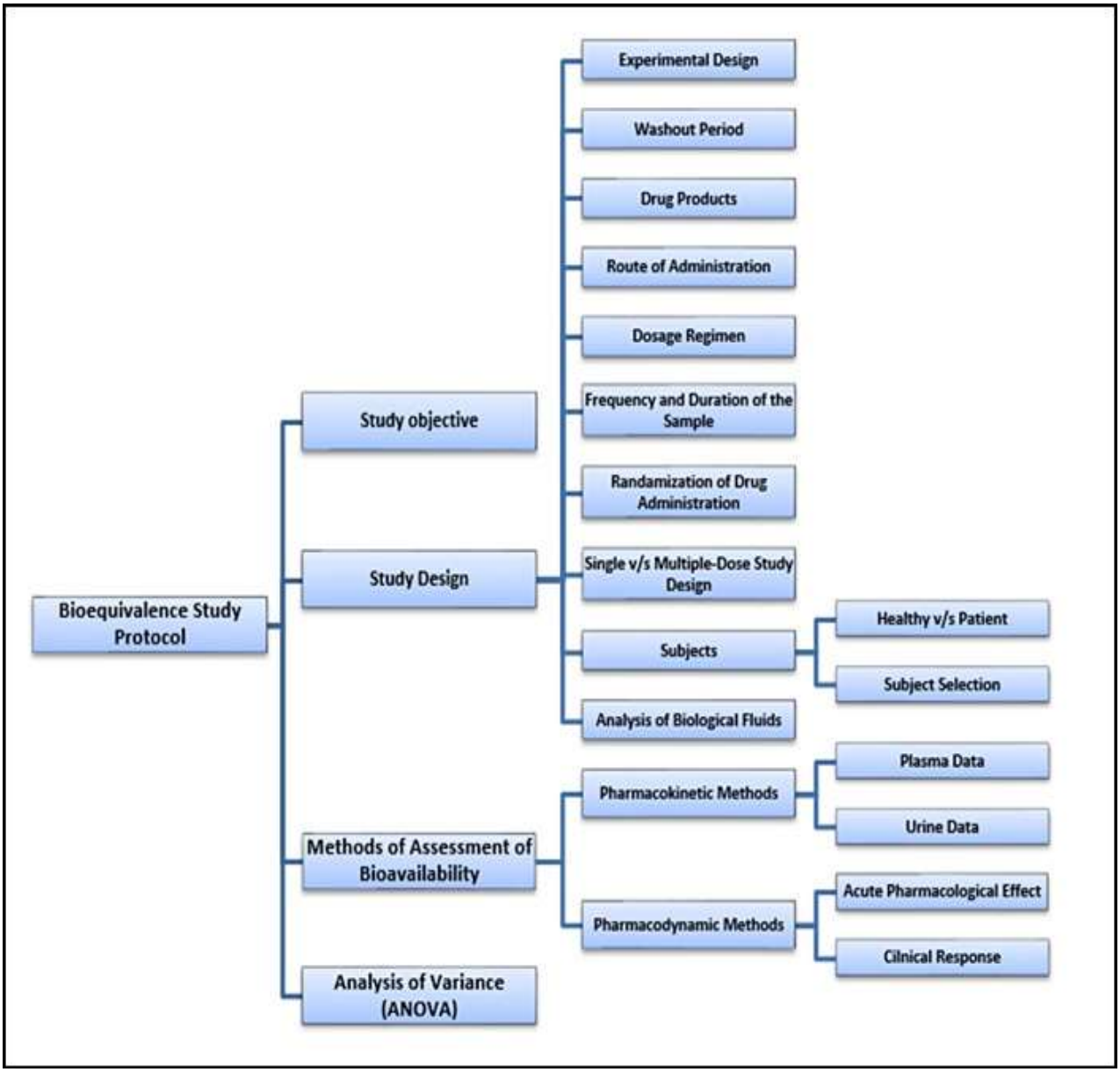

Fig 1: Elements of Bioequivalence Study Protocol

AIM AND OBJECTIVES

- The purpose of bioequivalence (BE) studies is to identify pharmaceutical equivalents or alternatives to be used interchangeably for the same therapeutic effect as a previously marketed drug. In general, we perform bioequivalence testing by comparing the bioavailability of the test product with the reference product.
- Establishment of bioequivalence is to demonstrate equivalence in biopharmaceutics quality between the generic medicinal product and a comparator medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the comparator medicinal product.
- Bioequivalence is determined based on the relative bioavailability of the innovator medicine versus the generic medicine. It is measured by comparing the ratio of the pharmacokinetic variables for the innovator versus the generic medicine where equality is 1.

An abbreviated new drug application (ANDA) contains data which is submitted to FDA for the review and potential approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, lower cost alternative to the brand-name drug it references.

Statistical analysis

The pharmacokinetic parameters AUC and Cmax 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 Cmax. 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 (H0) of non-bioequivalence at 5% level of significance (α=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 (H1) 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. H0 = bioequivalence, H1 = 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 (α=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 Cmax 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 (α=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).

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 parentral 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.

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 (Cmax) (Niazi, 2007; FDA, 2001a, 2003; Pidgen, 1996; Nation & Sanson, 1994).

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. No replicate 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; Steinijans et al., 1992; Metzler, 1989).

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).

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)

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).[9-15]

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.

Data analysis Data analysis is carried out:

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

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 (AUC0-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 (AUC0–∞) where AUC0–∞ = AUCt + Ct / λz Ct is the last measurable drug concentration and λz 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.

CONCLUSION

The Food and Drug Administration (FDA) is amending its regulations on the submission of bioequivalence data to require an abbreviated new drug application (ANDA) applicant to submit data from all bioequivalence (BE) studies the applicant conducts on a drug product formulation submitted for approval. In the past, ANDA applicants have submitted BE studies demonstrating that a generic product meets bioequivalence criteria in order for FDA to approve the ANDA, but have not typically submitted additional BE studies conducted on the same drug product formulation, such as studies that do not show that the product meets these criteria. FDA is amending the regulation because we now believe that data from additional BE studies may be important in our determination of whether the proposed formulation is bioequivalent to the reference listed drug (RLD), and are relevant to our evaluation of ANDAs in general. In addition, such data will increase our understanding of how changes in components, composition, and methods of manufacture may affect product formulation performance.

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REFERENCES

1. Banahan, B. F. & Kolassa, E. M. (1997). A physician survey on generic drugs and substitution of critical dose medications, Archive of Internal Medicine, 157, 2080-2088.
2. Benet, L. Z. & Goyan, J. E. (1995). Bioequivalence and narrow therapeutic index drugs, Pharmacotherapy, 15, 433-440.
3. Boix-Montanes A. (2011). Relevance of equivalence assessment of topical products based on the dermatopharmacokinetics approach, European Journal of Pharmaceutical Sciences, 42 (3), 173-9.
4. Central Drugs Standard Control Organization (CDSCO) (2005). Guidelines for bioavailability and bioequivalence studies. Directorate General of Health Services.
5. Ministry of Health and Family Welfare, Government of India, New Delhi. Available from: http://cdsco.nic.in/html/BE%20Guidelines%20Draft%20Ver10%20March%2016,%2005.pdf
6. Chen, M. L. & Lesko, L. J. (2001). Individual bioequivalence revisited, Clinical Pharmacokinetics, 40 (10), 701-6.
7. Chen, M. L. ; Patnaik, R. ; Hauck, W. W. ; Schuirmann, D.J. ; Hyslop, T. & Williams, R. (2000). An individual bioequivalence criterion: regulatory considerations. Stat Med, 19 (20), 2821-42.
8. Committee for Proprietary Medicinal Products (CPMP) (2000). Note for guidance on the investigation of bioavailability and bioequivalence, The European Agency for the Evaluation of Medicinal Products (EMEA) – Evaluation of medicines for human use. London, 14 Dec 2000 CPMP/EWP/QWP/1401/98. Available from: http://www.eme.europa.eu/docs/en_GB/ducument_library/Scientific_guideline/2009/09/WC500003519.pdf
9. Crawford, P. ; Feely, M. ; Guberman, A. & Kramer, G. (2006). Are there potential problems with generic substitution of antiepileptic drugs? A review of issue, Seizure, 15, 165-176.
10. FDA (1992). Guidance for industry, Statistical procedures for bioequivalence studies using a standard two-treatment crossover design. U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), July 1992. Available from:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072878.pdf

11. FDA (1996). Guidance for industry, E6 Good Clinical Practice: Consolidated Guidance. U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), April 1996. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073122.pdf
12. FDA (2000). Guidance for industry, Waiver of In vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research (CDER) August 2000. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf
13. FDA (2001a). Guidance for industry, Statistical approaches to establishing bioequivalence. U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), January 2001. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070244.pdf
14. FDA (2001b). Guidance for industry, Bioanalytical Method Validation. U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), May 2001. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf
15. FDA (2003). Guidance for industry, Bioavailability and bioequivalence studies for orally administered drug products – General considerations. U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research (CDER) March 2003. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf.