REFERENCE SCALED AVERAGE BIOEQUIVALENCE: SCALING APPROACH FOR THE HIGHLY VARIABLE DRUGS

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Abstract
Bioequivalence (BE) studies are an integral component of the new drug development process. Additionally, they are required for the approval and marketing of generic drug products. Bioequivalence studies are performed to demonstrate *in vivo* that two pharmaceutically equivalent products (in the US) or alternative pharmaceutical products (in the EU) are comparable in their rate and extent to which the active ingredient of active moiety becomes available at the site of drug action. By definition, for highly variable drugs (HVDs), the estimated within-subject variability is >30%. HVDs often fail to meet current regulatory acceptance criteria for average bioequivalence (ABE). The determination of the bioequivalence of HVDs has been a vexing problem since the inception of the current regulations. It is of concern not only to the generic industry but also to the innovator industry. This article reviews the definition of HVDs, the present regulatory recommendations and the approaches proposed in the literature to deal with the bioequivalence problems of HVDs. The approach of scaled ABE (SABE) is proposed as the most adequate procedure to solve the problem. It is demonstrated that SABE has firm theoretical foundations. In fact, statistical tests similar to SABE are used in various fields, such as psychology and quality control. Algorithms and numerical examples are presented to calculate SABE from the data in conventional replicate-design studies. The most important feature of SABE is that a fixed sample size is adequate to demonstrate bioequivalence regardless of within-subject variability. We have compared simple replicated design approach and reference scale average bioequivalence approach in this paper. The data is considered using 5% error from the actual study.
Keywords: Replicate, Scaled Bioequivalence, Highly variable drug, Intra subject Variability

INTRODUCTION

The width of the 90% confidence interval depends on the number of subjects in the study and the magnitude of the residual variance. The Analysis of variance-coefficient of variation (ANOVA-CV) is simply the square root of the residual variance multiplied by 100.

Highly variable drugs (HVDs) have been defined as drugs in which the within subject variability (WSV) in pharmacokinetics estimated from the ANOVA-CV equals or exceeds 30%. An advantage of replicate designs, in which the test and reference formulations are each administered twice is that the subject by formulation interaction can be 'teased out' of the residual variance and it is possible to estimate within subject variability associated with the test (Swt) and reference (Swr) formulations. For drugs with an expected within-subject variability of 30% or greater, a BE study with three-period, reference- replicated, crossover design with sequences of Test-Reference-Reference (TRR), Reference-Test-Reference (RTR), and Reference-Reference-Test (RRT) is proposed by the Food and Drug Administration (FDA). Specifically, subjects receive a single dose of the test product once and reference product twice. The objective of our research is to study the both the methods i.e. simple replicated design and reference scale approach.

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METHODOLOGY

We have considered error data from the two studies one is, randomized, open label, two treatment, three period, three sequence, single dose, reference replicated, crossover, reference-scaled average bioequivalence study in normal, healthy, adult, human subjects under fed conditions and other study was randomized, open label, two treatment four period four sequence, singe dose replicated average

bioequivalence stud in normal, healthy adult human subjects under fed conditions. Total of 66 and 160 subjects were enrolled for both the studies respectively. The pharmacokinetic analysis for the both the studies were performed using non-compartmental model of Winnonlin. The statistical analyses for both the studies were performed using SAS, Statistical software version 9.1.3. The Estimates, as well as 90% CI for simple replicated design and 95% upper bound of the confidence interval for the reference scaled replicated design were calculated.

RESULTS

As stated earlier, an advantage of replicate design is that data are provided on the within-subject variability of the test and reference formulations. One could surmise then that introduction of a better quality, less variable generic product would pose no hazard to the patient. Therefore we would recommend reference scaling be allowed when the reference formulation is a highly variable drug product.

DISCUSSIONS

This article presents a proposal for the BE evaluation of highly variable drugs and drug products. This new approach addresses many of the concerns about the BE of highly variable drugs/products that have been raised for the past several years. The proposed approach adjusts the BE limits of highly variable drugs/products by scaling to the within subject variability of the reference product in the study. The recommendation for the use of reference-scaling is based on the general concept that reference variability should be used as an index for setting the public standard expressed in the BE limit. Furthermore, for drugs and products that are highly variable, reference-scaling effectively decreases the sample size needed for demonstrating BE. The additional requirement of a point-estimate constraint will impose a limit on the difference between the test and reference means, thereby eliminating the potential that a test product would enter the market based on a bioequivalence study with a large mean difference. The use of the reference-scaling approach necessitates a study design that evaluates the reference variability, via multiple administration of the reference treatment to each subject. The recommended 3-period design is the most efficient way to obtain this information. The proposed approach will resolve a number of issues in the BE evaluation of highly variable drugs while achieving the FDA's mission of ensuring that all the drugs approved for use in U.S. are both safe and effective. One could summaries then that introduction of a better quality, less variable generic product would pose no hazard to the patient. Therefore we would recommend reference scaling be allowed when the reference formulation is a highly variable drug product.

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