Nontraditional Study Designs for Proving Bioequivalence

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From past many years, concerns have been expressed regarding meeting the standard bioequivalence (BE) criteria for highly variable drugs. This has been point of discussion in many conferences and meetings. But to date there is no as such regulatory definition for these drugs or drug products. To pass conventional goal posts for these drugs, the number of subjects required for a study can be much higher than normally needed for a typical BE study. The resources required and the ethical concerns of exposing large number of healthy volunteers to a test drug further poses challenge to the suitability of conventional BE criteria (with an 80-125% acceptance range) for highly variable drugs. Examples exist where a highly variable reference product failed to demonstrate BE when compared to itself in a bioequivalent study using the standard design/sample size.

Several proposals are available to modify the existing BE criteria for these variable drugs. A potential solution to the problem of highly variable drugs is suggested by the observation that most highly variable drugs have a wide therapeutic index. In general these criteria are based on either the reduction of the level of the confidence interval or an increase of the width of the equivalence limits or both. Various ways of appropriately widening the acceptance range for highly variable/ wide therapeutic index drugs have been discussed and investigated. Few of them are expanding BE limits based on sample size, reference variability and scaling. Partial replicate design allows for the estimation of within subject variability for the reference product. The approach that currently seems favored by scientists, researchers and regulatory authorities in the field is that of scaled average bioequivalence (SABE). SABE method is technically more demanding and required effort in the implementation, as the analyzed statistics cannot any more to be assumed to be normally distributed. 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 concept that reference variability should be used as index for setting the public standard expressed in the BE limit. Furthermore, reference scaling effectively decreases the sample size needed for BE study. Special linearization or boot strap methodologies are possible solutions for this.

The proposed approach will resolve issues in the BE evaluation of highly variable drugs while achieving the regulatory authorities mission by ensuring that all the drugs approved are safe and effective. Thereby securing and expanding opportunities for generic formulations in the future. There is also a need for all national regulatory agencies, especially in the emerging markets to align themselves and update regulatory approval processes, in accordance with the current international thinking on the subject.

References

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