POPULATION AND INDIVIDUAL BIOEQUIVALENCE
AAPS Bioequivalence Focus Group1
Position Statement

PAST SUCCESS OF ABE

Variations of the present ABE approach have been used internationally for 25 - 30 years.

- Until recently, the position of FDA was that no therapeutic failures have been reported for products approved on the basis of the present ABE approach.
- Post marketing surveillance has never suggested a clinical concern from ABE.
- No convincing data have appeared in peer-reviewed journals suggesting a clinical problem with ABE
- Recent concerns regarding BE have been raised based upon the advent of the statistical hypotheses behind PBE and IBE. The hypothesis was postulated and evidence of an application was then sought.
- The absence of therapeutic failures over a 25 - 30 year period using ABE should alleviate any concerns, especially those raised by nothing more than a statistical hypothesis.
- No change to the current ABE approach is anticipated anywhere else in the world.

INCREASED COMPLEXITY OF THE STUDY DESIGN

- The replicated design will increase the cost of BE studies (Clinical, Bioanalytical, and Data Analysis). This cost will be passed on to the patient.
- Dropouts will become a problem with the two additional periods.
- Safety issues will arise from the increased number of samples and the larger total

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1 AAPS Bioequivalence Focus Group is composed of a diverse set of pharmaceutical scientists from innovator and generic pharmaceutical industry, contract research organizations, academia, and consultant services.

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blood volume.

The expectation is that large groups of volunteers will be available for study-driven activities lasting twice the usual period of time and that they can be readily recruited to participate on the same dates. This is an unrealistic expectation as replicated design studies become larger and more frequent, and as special subgroups of the population have to be represented.

SUBJECT BY FORMULATION INTERACTION

If a meaningful subject by formulation interaction exists, a single BE study enrolling a relatively small number of subjects will have essentially no chance of consistently detecting it.

- There is no realistic way to assure the enrollment of a subset of subjects causing the subject by formulation interaction.
- Hypothetically, a subject by formulation interaction might be detected in one study but not in another, simply because the subset of subjects was not included?
- A subject by formulation interaction might be detected in one study but not in another purely by chance.

Current thinking is that $\sigma_D > 0.15$ suggests a significant subject by formulation interaction

- This value can exceed 0.15 due to nothing more than chance (random variation, etc?)
- It has been demonstrated that σ^2_D increases as $\sigma^2_{W,R}$ increases. Therefore, a large $\sigma^2_{W,R}$ might result in a false positive subject by formulation interaction.
- There is no evidence that $\sigma_D > 0.15$ implies clinical significance. What value of σ_D is truly consistent with a clinically relevant subject by formulation interaction? This would probably vary between drugs and between studies.
- Since the subject-by-formulation variance is a part of the residual error in the ANOVA of a two-period study, it cannot be large for drug products with low variability.

ALTERNATE APPROACH

It has been pointed out that concerns regarding variance differences (test vs reference) and subject by formulation interactions can be studied using the two-way crossover design with data analyzed by the method proposed by L. Gould. This method compares means, compares total variances (test vs reference) rather than within-subject variances, and assesses subject by formulation interactions (σ^2_D).It deserves further study. Applied to the existing FDA database (results of two-way crossover studies submitted over the past 25 - 30 years) this method could provide a reasonable assessment of switchability concerns resulting from variance differences (test vs reference) and/or subject by formulation interactions. Any reported problems could then be subjected to further testing to assess the clinical significance and the mechanism of the observed subject by formulation interaction. If the proposed re-analysis suggests a clinically significant problem due to variances differences (test vs reference) or subject by formulation interactions, an alternate analysis of the two way crossover study, based upon means, total variances, and σ^2_D, may be proposed. A change in methods, however, is not warranted until a clinically significant concern is raised by a re-analysis of the existing FDA database.

It would be interesting to separately estimate the within-subject variance of all test and reference products using the replicated study design. However this gets into a "nice to know" vs "need to know" situation. It is now clear that switchability can be established without a separate estimation of within-subject variance. Moreover, existing evidence does not suggest any problems with the present ABE method that compares means only.

It may be reasonable to ask an innovator company to conduct at least one replicated study and estimate the within-subject variance of a new product. There should be no

mandatory applications of the replicated study design during the ANDA process. The only concern is switchability and this can be addressed using a two-way crossover design with data analyzed by the method proposed by L. Gould. Again, concerns should be assessed using the FDA database prior to any change of existing methods.

Replicated study designs should be encouraged, but not required, for highly variable drugs and drug products. The current approach is inadequate because a relatively large number of subjects is often needed to achieve sufficient statistical power.

There is no need to conduct a replicated study for a low variability drug. This has been clearly demonstrated by studies submitted to the FDA in support of generic warfarin and other products.

NEED FOR FURTHER RESEARCH - TRIAL PERIOD

It has been pointed out in the past by the FDA and more recently by the industry that there is no evidence of therapeutic failures resulting from products approved on the basis of the existing ABE approach. After 25 to 30 years of drug product approvals based upon variations of ABE, the absence of such evidence should alleviate any potential concerns, especially those suggested by nothing more than a statistical hypothesis. A two-year trial period would increase cost, delay approvals, and would not yield any information that cannot be determined by a re-analysis of studies submitted over the past 25 years. The database is available and an adequate method has been proposed. In fact, the true objective of the two-year trial period was never clearly stated.

CONCLUSION

Because no clinical concerns have been raised and the proposed re-analysis is examining an issue suggested only by a statistical hypothesis, the present ABE approach, using the two-way crossover design, should remain in effect pending the outcome of the proposed re-analysis of the existing FDA database. This re-analysis should include a physiological (mechanistic) explaination of the hypothesized subject-by-formulation interaction. Regulation (Regulatory Guidelines) should be based on established knowledge and should not serve as a mechanism for testing a statistical hypothesis.