Individual Bioequivalence . . . Are we ready for it?

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Introduction

- While the proposed individual bioequivalency methodology may have some scientific merits, there are a number of unresolved issues regarding actual implementation and use.
- Ultimate adoption of the methodology may not prove to be in the best interest of the public.

Points of Issue:

- Is there a problem?
- Method is too complicated
- Disagreement on the mechanics of IBE
- S*F may be misinterpreted
- Limits on Ratios, contradicts the method
- Reduced population sampling
- May impede Generic competition
- Acceptance at the State Level
- Data already available

Is there a problem?

- Is the current methodology satisfactory for protecting the Public?
  - if so, should a change be implemented
  - if not, then where is the proof

A convincing case for IBE has yet to be made.

Method is too complicated

- The method and criteria can not be conveyed readily to the Public or even heath care professionals.
- Theoretically, information from a conventional 2-period crossover study may essentially give similar information as a 4-period replicate study [see method of Gould].

Disagreement on the mechanics of IBE

- From the recent AAPS co-sponsored workshop, there was apparent disagreement on proposed method.
- Even if one believes a new method is justified, little consideration has been given to alternate proposed methodologies.

S*F may be misinterpreted

- Subject-by-formulation can be affected by random variation.
- Certain types of outliers may mislead the interpretation, for example:

T T R R

What does S*F tell us

- One of the driving arguments for IBE has been to identify subject-by-formulation interactions, for example:

T T R R

- When this type of result occurs, it would appear to provide the same information as measured by ABE.

Limits on Mean Ratios, contradicts the method

- When the Test formulation is found to be less variable, then the criteria may be scaled to variability of the Reference. However, it is proposed that some limit on mean ratios be implemented, contradicting the method theory and reverting to a somewhat conventional interpretation. For some products, Reference-vs-Reverence ratios could be fairly divergent.

Limits on Mean Ratios (cont.)

- Limits on mean ratios, with IBE, might negatively affect the Public as follows:
  1) Pioneer may attempt to make formulations more variable.
  2) With the even tougher criteria, there might be fewer Generic formulations ultimately available.

Reduced population sampling

- Reducing the population sample from N=24 (ABE) to N=12 (IBE) also reduces the potential to see or identify subgroups showing significant differences between formulations.

May impede Generic competition

- For variable Pioneer drug formulations, there may be cases where only PBE passes.
- If we move forward with this method, then Pioneer should be held to similar requirements for any significant formulation changes, relative to clinical formulation, pre- or post- approved. IBE results should appear in labeling.

Acceptance at the State Level

- In certain states, where Formularies for substitution of Generic drugs exist, it is already a sometimes tenuous task to gain approval. How will these Formularies react to approvals under the proposed method.

Data already available

- There are already 55 - 60 replicate design data sets available. Will an additional 400 data sets significantly add to our understanding?
- Two-period crossover data sets might also be evaluated to determine if a problem really exists [see Gould].

Summary

- The problem may be stated in theory, convincing evidence is lacking.
- Method is too complicated, leading to implementation of multiple rules and conditions.
- In some instances, interpretation may be misleading, ex. S*F interaction.
- Potential to further evolve a Brand-defense tool.
- Data currently available to assess utility of method.

Conclusion

- A convincing case, that the Public will benefit from the methodology, cannot be made . . .

  based on existing data or even that envisioned for a trial period.