IGPA Position Paper on Individual Bioequivalence

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To Advisory Cmte For Pharm. Science

By

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Introduction

- IGPA is comprised of NAPM, NPA, GPIA, (US) EGA (Europe) and CDMA (Canada).
- The Conclusions of the Position Paper were presented at the AAPS/FDA Workshop on IBE, Aug 30, 1999 (Montreal)

Overall Assessment

- The scientific advisory committees of the member organizations of IGPA, along with other scientists within their respective companies and consultants from academia and private industry, have concluded:
  - the proposed changes lack sufficient scientific merit to justify the extensive clinical, technical and administrative changes, and the increased costs, that IBE would herald.

Conclusion 1

- The scientific and clinical basis for implementing a new system for the regulatory assessment of bioequivalence, employing the approach of "individual and population bioequivalence" has not been demonstrated.

Conclusion 1 A

There are no published studies in peer-reviewed journals, demonstrating that the currently applied approach of "average bioequivalence" is inadequate or that it is insufficient for determining the relative bioavailability of drug formulations in regulatory submissions.

- Many believe that the interesting concept of "switchability" has not been shown to have clinical relevance.

Conclusion 1 B

In particular, the view that subject-by-formulation interactions are substantially prevalent and constitute a regulatory concern, is not supported by published scientific data.

Conclusion 1 B (i)

- **Based upon the similarity in the release characteristics for the majority of products (IR) that demonstrate average bioequivalence, there is little scientific rationale to expect important s-b-f interactions for studies conducted under conditions of "average bioequivalence".**

Conclusion 1 B (ii)

- **Current understanding suggests that an observed $\sigma_D > 0.15$ might not represent a true s-b-f interaction (random variation, outliers, others?)**

Conclusion 1 B (iii)

If there were true s-b-f interactions detected under conditions of ABE, we have no idea of how large these would need to be to have any clinical significance whatsoever.

Conclusion 2

Newly proposed modifications of the methodology must be assessed by scientists in academia and industry before their possible adoption.

- several studies analyzed the approach proposed by the Preliminary Draft Guidance following its publication in 1997 and revealed serious deficiencies in the assumptions and methodology.

Conclusion 3

It is unnecessary to perform replicate-design studies with drugs exhibiting low residual variation in 2-period investigations of bioequivalence.

- The s-b-f interaction as well as the intrasubject variations of the two formulations are small with these drugs, and replicate-design studies would not yield additional useful information.

Conclusion 4

An interim experimental period for regulatory submissions, requiring a replicate design for all bioequivalence studies is unwarranted based on the current level of evidence. Such a directive would be disruptive to the industry and add a financial burden and time delay that will not be offset by a benefit of possible discoveries.

Conclusion 4 A

However, an interim experimental period might be reasonable for the regulatory submission of certain bioequivalence studies with replicate designs, if the selection of the products were limited to a few considered to have a scientific rationale for s-b-f interactions , or if they were at the discretion of the sponsor.

Conclusion 4 A (i)

To evaluate the probability of detecting s-b-f interactions, one could screen the large pool of currently available 2-period bioequivalence studies, retroactively. If screening were to reveal potential s-b-f interactions, these could be investigated further in prospective studies.

Conclusion 4 A (ii)

Any interim experimental period, even if only voluntary, must not be considered until there are clear statements regarding:

i) the purpose of the experiment;
ii) the study design;
iii) how the data will be analyzed;
iv) how the data will be used.

Conclusion 5

The current approach for assessing bioequivalence is inadequate for highly variable drugs because the number of studies needed to demonstrate equivalence is large and the number of subjects in each study is excessive.

Conclusion 5 A

This problem is not due to formulation differences among products, but is the consequence of highly variable drug disposition.

- **assess and implement approaches such as scaled regulatory criteria based on 2-period and replicate-design studies that would enable the effective determination of bioequivalence for highly variable drugs.**

Assessment of AAPS/FDA Workshop on IBE

- Overwhelming opposition to implementation of IBE
  - CRO's, who would gain financially, are even opposed on scientific issues and practical matters
- Such strong opposition should mandate a reissue of any plan that is intended to go forward as another Draft Guidance.