Consensus Report on "Issues in the Evaluation of Bioavailability"[1]

The symposium on "Bio International '89: Issues in the Evaluation of Bioavailability," held in Toronto, October 1–4, 1989,[2] resulted in consensus reports for three sessions:

(1) Rate of Absorption in Bioequivalence Determinations,
(2) Design and Assessment of Equivalency of Highly Variable Drugs (Session IV at the symposium), and
(3) Treatment of Bioequivalence Data (Session V at the symposium).

The following is a list of discussants together with the consensus statements.

SESSION 1: RATE OF ABSORPTION IN BIOEQUIVALENCE DETERMINATIONS

Topic 1. When Is Rate Important?

Chairperson. Dr. J. Skelly (USA).

Panel and Speakers. Drs. B. P. Imbimbo (Italy), W. R. Gillespie (USA), M. C. Meyer (USA), and J. M. Aiache (France).

Rate of absorption is known to be important

(1) where quick onset of pharmacological action is required, e.g., analgesics, hypnotics, and anesthetics;
(2) where it is known that the drug (i.e., antianxiety) needs to be dosed for some time before obtaining the desired therapeutic effect; and
(3) except in cases where it has been studied and shown to be of minor influence (clinical, pharmacodynamic).

Chairpersons (Topics 2 and 3). Dr. K. Murata (Japan) and W. J. Jusko (USA).

Topic 2. Methods of Determining Rate of Absorption: Advantages and Limitations.

Panel and Speakers. Drs. J. R. Crout (USA), P. T. Pollack (Canada), J. G. Wagner (USA) and G. Tucker (UK).

Assessment of drug absorption rates is of importance

(a) for agents with a low therapeutic index or a steep concentration/response curve,
(b) for formulations with sustained or special delivery rates,
(c) in any situation where it is necessary to exactly describe or predict the concentration versus time curve. Minimally, the C_{max} and T_{max} characteristics of *all* drug products should be evaluated unless it can be shown that these proprieties are irrelevant to therapeutic efficacy or toxicity of the drug.

C_{max} and T_{max}, along with AUC, are usually sufficient for assessing the bioequivalence of two products, although T_{max} is often difficult to determine accurately.

A broad array of methods exists for calculating absorption rates. Generally they are divided into curve-fitting, mass-balance, and deconvolution procedures. After summarizing the properties of an ideal method, Dr. Tucker recommended the deconvolution method of Proost.

Dr. Wagner demonstrated the utility of new calculation methods based on compartmental fitting of extravascular data. Dr. Jusko showed that the recently described area function method, a simplified form of point-area deconvolution, works as accurately as nonlinear least-squares curve fitting and is superior to moment analysis.

The general consensus was that additional comparative studies of various techniques are needed to assess recovery of assigned absorption rates under conditions where random variation is added to simulated data, including intraday variation in drug elimination.

No single method for calculation of absorption rates is recommended for regulatory purposes as various procedures require expert evaluation of oral and/or iv data.

Complicating factors include intraday variation in disposition, presence or absence of nonlinearity, availability of requisite computer software, and data itself, particularly during the absorption phase.

Topic 3. Special Statistical Considerations

Speakers/Panel. Drs. R. Nair (Canada), L. Endrenyi (Canada), S. Bolton (USA), K. Karpinski (Canada), and H. P. Wijnand (Netherlands).

Measures commonly used in bioequivalence assessments are the area under the plasma concentration–time curve (AUC), the maximum observed concentration (C_{max}), and the time when the C_{max} is reached (T_{max}). C_{max} and T_{max} are generally accepted as reasonable indicators of rate of absorption. These measures are relatively robust but are often observed to have large variances.

Designs can be considered which reduce the variability through optimal choice of sampling times but these attempts are likely to have limited success because of intrasubject and intersubject variability.

A variety of other procedures has been proposed to provide more direct and precise estimates of rate of absorption. Procedures include pharmacokinetic modeling, deconvolu-

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tion methods, physiological modeling, etc. These procedures have the advantage of specifically addressing the problem of estimation of rate of absorption.

However, these procedures are directed largely at precise characterization of concentration–time profiles using, to varying degrees, assumed absorption and elimination models, subjective judgment, and ancillary information. Statistical properties such as robustness, bias, and variance of estimate remain to be assessed.

Procedures aimed at testing differences in absorption rates without explicitly estimating the rate of absorption have also been discussed.

These include point-by-point testing, repeated-measures analysis of variance, nonparametric tests, etc. Problems with these approaches include multiplicity of testing and difficulties in interpretation of testing a hypothesis of no formulation differences, while the purpose of bioequivalence assessments is to demonstrate that the formulation differences are within clinically acceptable limits.

SESSION 2: DESIGN AND ASSESSMENT OF BIOEQUIVALENCE OF HIGHLY VARIABLE DRUGS

Chairpersons (Topics 1 and 2). Drs. P. duSouich (Canada) and J. T. Doluisio (USA).

Topic 1. Design Considerations: Crossover, Replicate, Parallel, Single Dose, Multiple Dose, Etc.

Panel and Speakers. H. Melander (Sweden), M. Yip (Canada), H. P. Wijnand (Netherlands), C. Petersen (Canada), and B. Cabana (USA).

Topic 2. Evaluation and Acceptance Criteria

Panel and Speakers. Drs. W. R. Gillespie (USA), H. P. Wijnand (Netherlands), R. Buck (USA), S. Dighe (USA), and O. Yoa-Pu Hu (Taiwan).

Definition of a Highly Variable Drug

Any drug that generates an intrasubject variability, as measured by the residual coefficient of variation, higher than 30%.

Sources of Variability

(a) Intrasubject variability secondary to the drug, formulation, and physiological factors of the subject
(b) Intersubject variability secondary to physiological factors

Solutions

(a) To Accommodate Intrasubject Variability
Depending on the drug, several options available are
- to increase the number of subjects
- to use a replicate design (complete or partial)
- to use multiple-dose design (steady state), especially when the drugs are used chronically or may present nonlinear kinetics
- to use stable isotopes, with a minimum of 12 subjects
- to use suitable pharmacokinetic correction methods

(b) To Accommodate Intersubject Variability
- rigorous inclusion and exclusion criteria
- when there are subjects unimodally distributed
  - cross-over design and classical analysis methodology
  - steady-state studies
- when the subjects are multimodally distributed
  - crossover designs
  - replicate designs
  - steady-states studies
  - analysis of data must take into account the multimodal distribution using nonparametric methods or parametric methods
  - optionally, identify a priori the outlying subjects and exclude them or include them, but taking exclusion criteria into account when designing the protocol and when analyzing the data

Acceptance Criteria

Use the confidence interval approach:
(a) with normal or log-normal distribution, use parametric tests;
(b) with neither normal nor log-normal data, use nonparametric tests.

Chairpersons (Topics 3 and 4). Drs. J. Thiessen (Canada) and U. Gundert-Remy (W. Germany).

Topic 3. Add-On Subject Designs

Panel and Speakers. Drs. K. Karpinski (Canada), C. Metzler (USA), L. Yuh (USA), and A. G. Rauws (Netherlands).

A bioequivalence study which has been properly planned and conducted may produce results which fail to satisfy regulatory bioequivalence standards. Additional experimentation may be carried out if there is a reasonable expectation that results from an add-on study, when combined with the initial study results, will provide the necessary data to satisfy regulatory requirements.

This approach assumes that there are no fundamental changes between the two studies in either formulations, design, analytical procedures, or subject populations. These assumptions should be validated using appropriate consistency checks, such as tests for formulation × study interaction and homogeneity of variances. The pooling of data should also be based on statistical procedures which are consistent with the study designs.

Topic 4. Design of Studies of Long-Half-Life Drugs

Panel and Speakers. Drs. W. Jusko (USA), A. Grahnen (Sweden), K. S. Albert (USA), and M. S. Yip (Canada).

There were two separate problem areas identified.

Practical Problems

(a) Availability of subjects involving long time period/long washout, dropouts, and ethical problems
(b) Interfering events involving disease, medication, and seasonal variation

Scientific Problems

(a) Intrasubject variability over time in the crossover design

Some proposed solutions were

(1) parallel design instead of crossover;
(2) patients and steady-state studies instead of volunteers; and
(3) if volunteers are used, truncated AUCs may be applied provided the postabsorption phase has been attained.

[See R. Urso and L. Aarons. *Eur. J. Clin. Pharmacol.* 25:689–693 (1973).]

SESSION 3: TREATMENT OF BIOEQUIVALENCE DATA

Chairpersons (Topics 1 and 2). Drs. D. S. Dighe (USA) and H. Melander (Sweden).

Topic 1. Log Transformation

Panel and Speakers. E. Ormsby (Canada), D. J. Schuirmann (USA), and Dr. L. Yuh (USA).

(A) There was no clear consensus on transformation. About one-third considered that log transformation for AUC and C_{max} should always be done. Another third thought it should never be done. The remaining third considered that, if statistical tests indicate transformation is appropriate, it should be done.
(B) It was evident that transformation needs more discussion by both statistical and pharmacokinetic experts.
(C) There is a need for education and communication on transformation to those to analyze, review, and/or use data from bioequivalence studies.

Topic 2. Outliers

Panel and Speakers. Drs. P. Veng-Pedersen (USA), S. Bolton (USA), N. M. Fleisher (USA), and S. Walters (Australia).

It was considered that

(1) Reasons for removal should
  (a) always be for a clearly documented experimental reason;
  (b) possibly be accepted because deviation so excessive that it appears probable that it is an artifact—POSSIBLY, and
  (c) *never* be because deviation is inconsistent with data
(2) The possibility that the "outlier" is actually contributing valuable information regarding the bioequivalence of the products should be considered.
(3) Recommendations
  (a) Regulatory agencies should define the special circumstances for which an outlier can be rejected.
  (b) Objectives tests and criteria should be developed by agencies.
  (c) Data analysis must include data base with and without outlier.

Chairpersons (Topics 3 and 4). Drs. Karim (USA) and K. Karpinski (Canada).

Topic 3. Significance of Sequence and Order Differences

Panel and Speakers. Drs. C. M. Metzler (USA), C. T. Rhodes (USA), F. R. Pelsor (USA), and H. Melander (Sweden).

(1) When sequence or period effects are found, an effort should be made to identify the cause (e.g., problems described by C. Rhodes).
(2) Some felt study designs, which contribute to an understanding/elimination of sequence/period effects, should be utilized more frequently.
(3) A study should not be rejected totally on the basis of statistically significant sequence/period effect.

Topic 4. Drug Content Normalization

Panel and Speakers. E. Ormsby (Canada), S. Bolton (USA), C. T. Viswanathan (USA), and I. McGilveray (Canada).

(1) Consensus agreement that AUC and C_{max} should be normalized for drug content of both dosage forms.
  (a) Most felt that, if possible, all studies should be conducted using doses which result in linear pharmacokinetics.
  (b) Most felt that data from both linear and nonlinear situations should be normalized. (Note: no time for simulations.)
(2) The group unable to agree on issue of requiring test and reference to be within 5%, i.e., lots selected vs normalization.
(3) Some believed USP-acceptable content range should be reduced for a drug like phenytoin with nonlinear kinetics in the therapeutic drugs.

Other sessions, for which no attempt at consensus was planned, were "Food Effects in Bioequivalence Evaluations," "Non-Systemic Drug Equivalence Issues," and "Analytical Issues in Bioequivalence Determinations." Arising from the analytical session is the idea of a bioanalytical workshop directed at bioequivalence, bioavailability, pharmacokinetic, and therapeutic drug monitoring validation and quality-control requirements which was held in Washington, D.C., in December, 1990.