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Conference Report[1]

Bio-International '92, Conference on Bioavailability, Bioequivalence and Pharmacokinetic Studies

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Organized by International Pharmaceutical Federation (FIP) together with American Association of Pharmaceutical Scientists (AAPS), U.S. Food and Drug Administration (FDA), and Health Protection Branch, Canada (HPB). Cosponsored by Bundesgesundheitsamt (BGA), Germany, European Federation of Pharmaceutical Sciences (EUFEBS), Academy of Pharmaceutical Sciences and Technology, Japan (APSTJ), Dutch Medicines Evaluation Board (RIVM), The Netherlands, and Zentrallaboratorium Deutscher Apotheker (ZL), Germany.

This report summarizes the discussions and statements of the Bio-International '92 conference concerning the topics highlighted at the sessions on

- bioequivalence of highly variable drugs (sessions I and II),
- importance of metabolites in assessment of bioequivalence (session II), and
- determination of food effects in bioequivalence studies (session IV).

The objective of Bio-International '92 was to take up some key issues raised in former conferences such as Bio-International '89 in Toronto and the Drug Information Association (DIA) meeting on bioavailability/bioequivalence in Barcelona in 1991. Scientists from regulatory bodies, control laboratories, academia, and industry, interested in and experienced with the topics were invited to contribute to the open discussions regarding the state of science and technology in this field.

The purpose of this report is to indicate the resolved and unresolved issues discussed during the conference, suggesting areas where consensus might be reached in the current international and interdisciplinary discussion of the scientific community interested in these issues. In addition, more controversial problems are better defined and strategies suggested toward their resolution. The document is based on the statements developed by panels during the conference summarizing presentations and discussions of the scientific sessions. Panel position statements were presented during the final session for comments by all participants and subsequently modified to take account of relevant arguments raised.

[1] To reach a wider distribution, and to have information available to scientists, by prior arrangement, this document was concurrently submitted to the following journals for publication: *European Journal of Drug Metabolism and Pharmacokinetics, European Journal of Pharmaceutical Science, International Pharmacy Journal, Journal of Pharmaceutical Sciences,* and *Pharmaceutical Research.* The article is part of *Proceedings of Bio-International,* Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, Germany.

SESSION I: BIOEQUIVALENCE OF HIGHLY VARIABLE DRUGS (I)

Chairpersons:	*H. H. Blume, R. L. Williams*
Panel and Speakers:	*L. Z. Benet, R. H. Barbhaiya, U. Gundert-Remy, H. Melander, K. K. Midha, E. Ormsby, A. E. Till*
Rapporteur:	*R. L. Williams*

A.1. Alternatives for Study Design in the Case of Highly Variable Drugs

A single, arbitrary set of bioequivalence acceptance criteria was previously agreed upon, which is intended to apply to all products. In some cases, however, it has been difficult to meet these criteria in experiments with a reasonable number of subjects. This may be, at least in part, a function of high intrasubject variability of the drug itself and/or from the drug product.

The definition of high intrasubject variability of pharmacokinetic data, proposed at the Bio-International '89 conference, was confirmed: drugs which exhibit intrasubject variabilities of more than 30% (CV_{ANOVA}) are to be classified as highly variable. However, in certain cases problems will sometimes occur also with lower variabilities, e.g., 25% CV.

Currently, as stated in 1989 in Toronto, we attempt to overcome the difficulty of assessing the bioequivalence

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of highly variable drugs with a reasonable number of volunteers with the following study designs (for example).

1.1. *Multiple-dose studies* are appropriate to dampen intrasubject variability and generally requested for drugs that exhibit nonlinear kinetics. Compared with the results of single-dose studies, intrasubject variability of data will normally be reduced by investigating the product(s) at steady state. Thus, it was shown experimentally that the CV_{ANOVA} for AUC values dropped from 34 to 15% in the case of a propafenone immediate-release product or for C_{max} values from 49 to 23% in the case of a verapamil immediate-release tablet formulation when preparations were studied after multiple dosing compared with the single-dose situation. In any event, a multiple-dose study design is generally required in the case of compounds exhibiting nonlinear pharmacokinetics.

1.2. *Replicate design studies* are requested to evaluate intrasubject variabilities of pharmacokinetic characteristics of the substance/product(s) under investigation. This may reduce the number of subjects required for a study but will not reduce the number of dosings.

1.3. *Stable isotope studies* are an appropriate way to reduce the number of subjects needed to assess bioequivalence. However, such studies are technically difficult and expensive, with 12 subjects considered as the lowest number of volunteers. Furthermore, a formulation containing the active ingredient with a stable isotope label cannot be manufactured in a normal production batch size.

1.4. *Group sequential studies* (add-on subject design) may be acceptable when designed prospectively with planned interim analysis and proper adjustment of significance level as necessary and appropriately stated in the protocol. Group sequential studies are not acceptable if data originating from separately performed investigations are to be combined in one single data set to assess bioequivalence.

In some cases, however, the above approaches may not sufficiently decrease the number of subjects required for the assessment of bioequivalence under the present acceptance criteria.

A.2. Other Alternatives

Within the existing concept of bioequivalence, there are two alternatives for further reducing the number of subjects needed to document bioequivalence. These should be understood as suggestions to be examined in addition to methods 1.1–1.4, not to replace them.

2.1. Widen the bioequivalence interval.

2.2. Reduce the level of the confidence interval.

The panel has concerns with the arbitrary application of either of these alternatives, as the consumer risk is increased in both cases.

A.3. Role of Variability of the Reference Product

The panel does, however, believe that there may be some value in seriously considering the possibility of varying the confidence interval acceptance criteria in accordance with the intrasubject variability of the reference product and/or expanding bioequivalence intervals based on pharmacodynamic considerations.

The panel recommends that these approaches be rigorously evaluated for.

3.1. Compatibility with minimizing consumer risk.

3.2. Feasibility of application.

3.3. Appropriate methodology.

3.4. Regulatory implications.

SESSION II: BIOEQUIVALENCE OF HIGHLY VARIABLE DRUGS (II)

Chairpersons:	*A. C. Cartwright, J. P. Skelly*
Panel and Speakers:	*M. Eichelbaum, J. H. G. Jonkman, J. Kuhlmann, G. Mikus, A. Rauws, F. Stanislaus, R. L. Williams, A. Yacobi, L. Yuh*
Rapporteur:	*J. Skelly*

B.1. Evaluation of Bioequivalence of Enteric-Coated Products

The discussion was limited to the bioequivalence of generic products. The assumption made is that the reference preparation has demonstrated clinical efficacy. For comparison of generic products to reference enteric-coated formulation, further restriction was made to maintain the same dosage form, i.e., single unit to single unit or multiple unit to multiple unit. Parameters defined to be studied are AUC, C_{max}, and t_{lag}, with the following limits.

1.1. AUC: 90% confidence interval (Schuirman's two one-sided test procedure), within 80–125%.

1.2. C_{max}: 90% confidence interval (Schuirman's two one-sided test procedure), within 80–125%.

1.3. t_{lag}: mean_{Test}, within 50–150% of $\text{mean}_{Reference}$.

There was some controversy concerning the estimation of t_{lag}.

Comment: Sessions I and II both dealt with bioequivalence of highly variable drugs, but from different viewpoints. Session II discussed only a very narrow theme and was, therefore, able to suggest definite limits. Session I tried to explore new ground. Therefore, it offered the opportunity to examine limits of criteria (see points A.2 and A.3). Sessions I and II should therefore be understood as mutually supportive, not contradictory, i.e., considerations in session I can be adopted under the limits B.1.1, B.1.2, and B.1.3 above.

B.2. Reference Product to be Chosen in a Bioequivalence Study

2.1. Where there is a single reference product (innovator), a two-way crossover design would compare test product to that of innovator.

2.2. Where there is more than one innovator product, the design would be a three-way crossover with
(a) solution (for insoluble drugs, a suspension),
(b) local innovator (one only),
(c) test product.

The name of the reference product is to be cited in the study report.

B.3. Significance of Reference Products in Bioequivalence-Evaluations

Prior to study, all products (test and reference) to be tested in the investigation have to be crosschecked concerning (bio)pharmaceutical quality. Batches selected for the study must be representative for product quality.

3.1. Small differences may be recognized between various reference products within and between countries.

3.2. During transition to a common reference, the national innovator reference product should be used, as, for this, it is accepted that clinical effectiveness is proven.

3.3. If there is no reasonable marketed product, a solution or suspension may be used.

As the final goal, full clinical data on reference products and fully characterized pharmacokinetic/biopharmaceutic information must be available.

B.4. Phenotyping in Bioequivalence Studies

Two situations are to be differentiated: new drugs and generics.

4.1. For bioavailability studies of new drugs (NCE, NAS) the determination of phenotype is required.

4.2. For generic drugs it is assumed that it is already known whether there is genetic polymorphism:
4.2.1. If there is no genetic polymorphism, no phenotyping is required.
4.2.2. If genetic polymorphism has been established, phenotyping of subjects is required in cases of
(a) single-dose studies with scientific rationale, i.e., where safety is a concern;
(b) multiple-dose studies.

For ethical reasons poor metabolizers should not normally be exposed to multiple-dose studies. There was no clear consensus regarding the inclusion or exclusion of "poor" or "extensive" metabolizers in other situations, e.g., to reduce variability.

B.5. Can We Fix Norms for C_{max} Confidence Intervals?

Fixing limits for C_{max} was a highly controversial topic. While the regulatory authorities in Europe and North America have agreed on acceptance criteria for the extent of bioavailability (AUC range, 80 to 125%; 90% confidence intervals), there is still some disagreement concerning C_{max}.

At Bio-International '92 and elsewhere, there has been renewed discussion of this issue, especially for highly variable drugs. By employing a replicate study design, as recommended by panel I, more information on C_{max} variations should be obtained for a greater number of marketed innovator products. Rationale decision criteria may be established based on such information.

Meanwhile, the panel, having a concern that the C_{max} criterion for generic products should not be more restricted than that for innovator products, offers the following interim recommendation:

> Studies with highly variable drugs should be performed in a replicate design. If the reference product, after such administration, meets a wider (than 80–125%, 90% confidence interval) C_{max} range, this wider range should also be used for the assessment of bioequivalence of the generic test formulation in comparison to the reference product.

SESSION III: IMPORTANCE OF METABOLITES IN ASSESSMENT OF BIOEQUIVALENCE

Chairpersons:	*L. P. Balant, K. K. Midha*
Panel and Speakers:	*S. V. Dighe, D. D. Breimer, W. Hauck, I. J. McGilveray, E. Mutschler, B. Scheidel, T. Suga, G. T. Tucker*
Rapporteur:	*L. P. Balant*

C.1. What Should be Required?

(i.e., What do regulators need to know vs feel would be nice to know and want to know?)

Only information necessary for decision making about the rate and extent of systemic availability should be used in the context of bioequivalence studies. From this point of view, measurement of the parent drug remains the method of choice in order to derive the bioequivalence characteristics needed for decision making on the rate and extent of absorption of a medicinal product as compared to a reference product.

C.2. Use of Metabolites: The Clear Cases

2.1. Inactive prodrugs with rapid biotransformation Measurement of concentrations of biotransformation products is essential if the substance is an inactive product which is rapidly biotransformed into an active metabolite responsible for efficacy and eventual toxicity.

2.2. Parent compound cannot be measured

If, for one reason or another (e.g., instability in the biological matrix, major difficulty in chemical analysis), it is impossible to measure concentrations of the parent compound, a major biotransformation product should be used.

In the EC Note for Guidance (1991) it is not necessary that such a major biotransformation product have demonstrated pharmacological activity.

C.3. Metabolites in Intermediary Situations

3.1. Clinical pharmacokinetics, bioavailability, and bioequivalence

The measurement of metabolites in addition to that of the parent compound always brings additional information. Such information is critical in the context of clinical pharmacokinetics, important for bioavailability considerations, and marginally useful in exceptional cases in the context of decision making in bioequivalence issues (see point C.1).

3.2. Definition of major-active metabolites

Although no precise rules can be set for the definition of what a major-active metabolite is, some conclusions and recommendations may be made at this point.

(a) Clinical activity of metabolites is usually unknown, and qualitative or quantitative pharmacological activity cannot be reliably extrapolated from animals to humans. Potency quantification of metabolites must be available in humans for decision making; the same is true for receptor specificity.

(b) The potential importance of a metabolite must be analyzed in the context of its receptor selectivity, intrinsic potency, relative blood or plasma concentrations (in relation to parent drug concentrations), and relative concentrations at the site of action (e.g., central nervous system). This also implies relative residence time in blood or plasma and at the site of action.

(c) More work is needed in the field of pharmacokinetic and pharmacodynamic relationships in order to clarify the above-mentioned aspects on the relative importance of metabolites. In the meantime, metabolite data should be used in the field of bioequivalence only when an advantage in decision making can be gained by such measurements.

3.3. Interindividual and intraindividual variability

As with parent compound variability, the situation is far from clear for metabolites (in particular, concerning intraindividual variability). From computer simulations (Dr. Tucker) it appears that, depending on the relative importance of metabolite clearance and renal clearance, and their intrasubject variation, plasma concentrations of metabolites may be more "stable" in the face of day-to-day variability than those of parent compound, and the opposite is true.

More research is needed before this matter can be resolved. This work should be both theoretical, using computer simulations, and experimental, by examination of real clinical pharmacokinetic studies. This is an important part of the "want to know" part of the problem.

3.4. Experimental design

Issues related to time of blood sampling in view of different elimination half-lives or t_{max} values should be further investigated in the context of bioequivalence studies. This is particularly true for the extrapolated part of the AUC to infinity and C_{max}.

3.5. Decision making

In view of the "need to know, nice to know, and want to know" concept, it would seem that in a majority of cases of decision making, evaluation should be based on parent compound bioequivalence characteristics.

> [It must be realized that adding bioequivalence characteristic of two or three metabolites or even one (e.g. AUC-confidence intervals) will lower the "consumer risk" below the stared 5% used for each characteristics. However, the exact effect of such additions on accepted risk threshold levels remains to be determined.]

In general, concern was raised by the conference participants that regulatory requirements related to metabolite data should not be increased, as long as the potential benefit of metabolite bioequivalence characteristics is further clarified in the context of decision making in bioequivalence studies.

The question was raised if metabolites characteristics shown a priori to be more stable than the parent compound could be used on a "pick out the best" basis. In such a case it is strongly recommended, if possible, to consult regulatory authorities before making this decision at the time of protocol writing. Such a decision made a posteriori would certainly not be acceptable in the great majority of cases.

C.4. Miscellaneous Issues

Some problems were touched on but were not extensively discussed. They are cited only briefly here.

4.1. Enantiomers

The use of specific analytical methods was briefly discussed. Two aspects must be taken into account:

(a) systemic availability of the two enantiomers and

(b) systemic clearance.

It was felt that if the two enantiomers are documented to show no difference for these two pharmacokinetic characteristics, a nonspecific method may be used. The choice of such a method must, however, be clearly documented in the report.

4.2. Nonlinear kinetics

Metabolites formed by a capacity-limited process but eliminated by a first-order process could be a useful alternative in order to overcome AUC nonlinearity as a function of dose. Such a choice should clearly be documented a priori.

C.5. Important Open Questions Raised During Discussion

5.1. How much do we know presently about the contribution of metabolite safety and efficacy issues?

5.2. If the parent compound and metabolite bioequivalence characteristics are used in the decision-making process, what would be the outcome if one of the two fails to reach statistical requirements and the other does not?

5.3. What is the situation if metabolites do not contribute to the therapeutic efficacy (e.g., toxic biotransformation products)?

C.6. Preliminary Conclusions

In the present state of our knowledge, no general rules or guidelines can be given for inclusion of metabolite data in bioequivalence assessment. In view of the extraordinary diversity of metabolic patterns of xenobiotics, it is unlikely that it will ever be possible to make such formalized recommendations.

The panel thus concluded that the rationale to include metabolites in bioequivalence decision making should, from case to case, be based on scientific knowledge and ethics, and not on arbitrary and general rules.

SESSION IV: DETERMINATION OF FOOD EFFECTS IN BIOEQUIVALENCE STUDIES

Chairpersons:	*J.-M. Aiache, P. G. Welling*
Panel and Speakers:	*D. J. A. Crommelin, B. Edgar, A. Karim, T. Nagai, R. Patnaik, T. Salmonson, V. W. Steinijans*
Rapporteur:	*A. Karim*

D.1. When Are Food Effect Studies Needed?

Food studies are to be understood as a measure of quality control on the product.

1.1. Food studies are necessary in the case of formulations with controlled/modified-release characteristics, including enteric-coated products.

1.2. Food studies are relevant for both innovator and generic preparations.

1.3. In the case of new chemical entities, drug formulations with immediate (=conventional) release also have to be studied for food effects.

1.4. The information derived from the results of food effect studies should be incorporated into labeling.

1.5. The procedure for already marketed products is somewhat different. For a new generic version the food effect investigations are necessary only if the records (label, literature) demonstrate the occurrence of food effects.

D.2. Food Effect Studies with Immediate-Release Formulations of New Chemical Entities (NCE)

For immediate-release formulations in the early stages of drug development the studies are needed to determine whether the food effects derive from the dosage form, the drug itself, or both.

2.1. In a two-way crossover single-dose pilot study the clinical supply formulation of the NCE (immediate-release formulation) is investigated after fed vs fasting administration. In the case of an observed food effect a NCE solution is subsequently studied in the fed vs fasting state.

2.2. In a second three-way crossover single-dose study for regulatory submission, the following administrations are to be investigated:
(a) clinical supply fasted vs
(b) market image fasted vs
(c) market image fed.

When a food effect is observed after single-dose administration, there was controversy as to whether or not a subsequent steady-state study is needed. Moreover, the effect of time of food intake relative to the drug dosing may need to be evaluated. Finally, this has to be decided case by case.

D.3. Food Effect Studies with Controlled/Modified-Release Formulations of NCE

3.1. In a four-way crossover pilot company study, clinical supply formulation and an oral solution (or if impractical, immediate release formulation) are investigated, both administered once in the fasted and once in the fed state.

3.2. In a subsequent three-way crossover investigation for regulatory submission the following administrations are to be studied:
(a) clinical supply fasted vs
(b) market image fasted vs
(c) market image fed.

In the case of food effects, observed after a single dose also for controlled/modified-release dosage forms, it is to be decided case by case whether a steady-state study in fed and fasted conditions is necessary.

D.4. Food Effect Studies for Generic Formulations (Bioequivalence Studies)

4.1. Food effects on generic products should be examined after single-dose administration under same conditions as the innovator's product. The suggested study design is a four-way crossover study investigating
(a) innovator fasted vs
(b) generic fasted vs
(c) innovator fed vs
(d) generic fed.

4.2. Alternatively, two separate two-way crossover single-dose studies might be performed investigating both innovator and generic formulations under fasted or fed conditions, respectively.

D.5. Standardized Conditions for Food Effect Studies

5.1. "Fasted state" means administration of the dosage form together with a fixed volume (120–240 mL) of water after an overnight fast for 10 hr or more. A high-fat breakfast is served 4 hr after dosing; no beverages are permitted for 4 hr after dose.

5.2. "Fed state" means administration of the dosage form together with a fixed volume (120–240 mL) of water immediately (within 15 min) after completing a high-fat breakfast, which is served after an overnight fast of about 10 hr and completed in about 30 min. Lunch should be given approximately 4 hr after dosing. It is recommended that no beverages be permitted for 4 hr after dosing.

5.3. An "international standard meal" is not needed—only a definition of carbohydrate, fat, protein, and caloric content. The issue of the composition of water (with or without minerals?) remained unresolved.

D.6. "Lack of Food Interactions," Labeling

Assessment of "lack of food interaction" has to be handled as an equivalence problem, with "test" as nonfasting and "reference" as fasting administration.

6.1. The standard equivalence range will be 0.8–1.25, 90% confidence intervals, unless modified by the innovator on clinical grounds. Any equivalence range modified from 0.8 to 1.25 must be stated in the labeling. The modified equivalence will then also be granted to generic manufacturers when they test their products.

6.2. "Lack of food interaction" is concluded if the 90% confidence interval for the ratio of expected medians for test and reference is completely in the equivalence range.

Comment: Different opinions for criteria of bioequivalence and food studies were stated at this conference. It was argued that food effect studies are conducted in order to obtain information for labeling purposes, whereas bioequivalence studies are carried out to meet stated regulatory criteria. In food studies attention has to be paid to clinical use (e.g., cholesterol inhibiting agents) and quality control of a dosage form. Major controversies arising from questions were FDA's concern that, for generics, a three-way "observational" study for "lack of food interaction" should suffice, i.e., not a rigorous statistical criterion. In addition, the NCE proposal was criticized as not being clinically relevant. Dr. Karim, however, noted that in a QC setting, it is the performance of the dosage form that is assessed. Any clinical concern would be addressed in efficacy studies, but major differences between clinical trials and market image formulations should be known.

OTHER SESSIONS

Other issues, for which no attempt at position statements was planned, were "Bioequivalence Studies: Disease State, Target Population, and Pharmacodynamics," "Superbioavailability," "Bioequivalence of Dermally Administered Drugs for Local Action," and "Individual Versus Average Bioequivalence," presented and discussed in the final session of the conference.