Midha • Nagai

Bioavailability, Bioequivalence and Pharmacokinetics Studies

F.I.P. Bio-International '96

Business Center for Academic Societies Japan, Tokyo

Bioavailability, Bioequivalence and Pharmacokinetic Studies

FIP Bio-International '96

International Conference of F.I.P. "Bio-International '96"
Tokyo, Japan, April 22–24, 1996

Edited by

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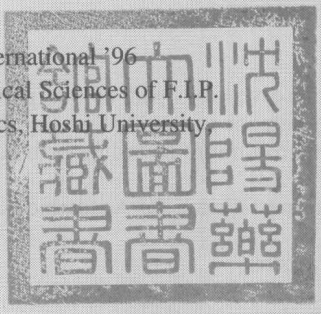

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Preface

The Conference (FIP BIO International '96) was held in Tokyo, Japan, April 22–24, 1996. It was a sequel to BIO International '94 (Munich, Germany), BIO International '92 (Bad Homburg/Frankfurt, Germany) and BIO International '89 (Toronto, Canada). Like BIO International '94 and '92, BIO International '96 and its post conference workshop, Bioanalysis '96, were organized by Fédération Internationale Pharmaceutique (FIP) and co-sponsored by Academy of Pharmaceutical Science and Technology Japan (APSTJ), American Association of Pharmaceutical Scientists (AAPS), Dutch Medicines Evaluation Board (DMEB), European Federation of Pharmaceutical Sciences (EUFEPS), Health Protection Branch, Health Canada (HPB), Japan Pharmaceutical Manufacturers Association (JPMA), Japan Pharmaceutical Association (JPhA) and The Pharmaceutical Society of Japan (TPSJ) in cooperation with the Ministry of Health and Welfare (MHW, Japan) and the United States Food and Drug Administration (US FDA).

The BIO International '96 was the First Asian Meeting. The objectives of BIO International '96 were: 1) to bring the debate on issues of bioavailability (BA) and bioequivalence (BE) into an Asian theater; 2) to build upon foundations laid by previous meetings of this type such as BIO Internationals '89, '92 and '94; and 3) to continue to move towards global harmonization of BA/BE issues where appropriate.

This volume contains the presentations given at the main conference of BIO International '96. There were six sessions and the tone of the conference was established by four keynote lectures. The topic of Session I, "Current Practice of BA/BE Requirements for Immediate Release Products in Different Countries" had ten presentations from representatives of Australia, Canada, China, Germany, Japan, Korea, Sweden, Taiwan/China, Thailand, USA and European Union, which were delivered with international harmonization in mind, whilst also recognizing the need for considerations given to specific regional requirements that arise, for example, as a result of differences in climatic conditions and ethnicity.

Session II considered "BE of Highly Variable Drugs and Drug Products: General Session, Individual Bioequivalence and Statistical Considerations", associated with the approaches to resolve their issues. In this Session presentations focused on their definition, experimental and statistical approaches involving single and multiple doses with replicate designs, and the status of individual bioequivalence. The debate was current and discussed issues which have been highlighted in other meetings and workshops on this specific topic.

Session III was devoted to Special Topics under which presentations concentrated on semisimultaneous administrations, stable isotopic methodology in BE studies, assessment of BE based on pharmacodynamic end points, and assessment of BE of topical products.

Session IV focused presentations on "Metrics and Alternative Approaches for BA/BE Studies" which considered measures of extent and rate of absorption as well as shape analysis of plasma concentration time curves.

Session V covered the topic "BA/BE of Extended and Controlled Release Products"

in which speakers covered food effects in BE studies of these products, importance of food effects in early drug development, regulation versus need, food and drug interactions in clinical practice and considerations in future development.

In Session VI "The Role of *In Vitro* Dissolution Test" was covered by viewpoints from Japan, US FDA and European Union. Acceptance of dissolution as a surrogate for BE for specialized cases and for certain changes in formulation and manufacturing process was discussed with a view to pinpoint differences and similarities among different regulatory and professional bodies. FIP dissolution guidelines for immediate release products, forthcoming Japanese dissolution guidelines and US FDA acceptance of dissolution under certain situations based on "Scale Up and Post Approval Changes (SUPAC)" were covered with a view to approach harmonization.

This conference like the previous ones was organized to allow exchange of ideas, information and view points among scientists from regulatory bodies, industrial research laboratories, academia and institutes with prospects to encourage and develop consensus on BA/BE issues in an open forum. It is a pleasant and satisfying feeling to see that BIO-International conferences have developed a clientele of committed scientists who give their time freely and participate with a spirit to cooperate and harmonize issues in BA/BE. There were more than 450 scientists who participated in the BIO International '96 Conference from 14 countries.

These Proceedings contain the statements of the conference on critically important issues resolved and highlight areas where further discussions and research need to be focused. We believe and trust that this volume will result in improved understanding of the BA/BE issues which are current as well as those where resolutions have been achieved. We all wish to have regulations which are based on good science and understanding of the complexities related to BA/BE. This volume presents the state of the art in BA/BE as understood and practiced today.

We are indebted to the invited speakers, rapporteurs, panel members, co-chairs of the sessions, and co-chairs and members of the Scientific Planning Committee, co-chairs and members of the Advisory Committee, chair and members of the Local Arrangement Committee, who gave their valuable time which made the BIO International '96 conference successful both professionally and socially. The publication of the Proceedings is the result of the efforts of all the committees mentioned above but more so, the prompt response of the invited speakers who completed their manuscripts within the deadlines set by the Conference co-chairs.

Our special thanks to Mr. Hitoshi Yamazaki and Ms. Noriko Uehara who superbly and efficiently managed the FIP BIO International '96 Secretariat. We are also indebted to Ms. Darlene Metz of the Drug Metabolism Drug Disposition Group, College of Pharmacy and Nutrition, University of Saskatchewan, who most efficiently assisted and managed the interface between Saskatoon (Canada) and Tokyo (Japan) and made undaunting efforts to see that these Proceedings got completed in time.

Kamal K. Midha
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Bio-International '96

Organized by: Board of Pharmaceutical Sciences, Fédération Internationale Pharmaceutique (FIP)

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Contents

Conference Report

Bio-International '96, Conference on Bioavailability, Bioequivalence and Pharmacokinetic Studies Tokyo, Japan, April 22–24, 1996

Kamal K. Midha, Tsuneji Nagai, Henning H. Blume, John W. Hubbard, Iain J. McGilveray, and Roger L. Williams

The objectives of Bio-International '96 were (i) to bring the debate on issues of bioavailability (BA) and bioequivalence (BE) into an Asian theater, (ii) to build upon foundations laid by previous meetings of this type such an Bio-Internationals '89, '92 and '94(*1–3*), and (iii) to continue a move towards global harmonization in issues relating to bioequivalence. This report is based on position statements from six panels whose task it was to focus the presentations and discussions during the six sessions of the meeting. The purpose of this report is to summarize issues resolved at this conference and to highlight questions remaining unresolved.

The tone of the conference was established by four keynote lectures as follows (in order of presentation):

- Problems and Progress: From Bio-International '89 to the Present.
  Prof. Leslie Z. Benet, University of California, USA
- Bioequivalence Assessment: Irrationality within a Rational Science.
  Prof. Gerhard Levy, State University of New York at Buffalo, USA
- The Regulatory Perspective: Japan.
  Dr. Yoshinobu Hirayama, Ministry of Health and Welfare, Japan
- The Regulatory Perspective: USA.
  Dr. Roger L. Williams, Food and Drug Administration, USA.

Salient points from these four important lectures were discussed on various occasions in the conference.

Session I: Current Practice of BA/BE Requirements for Immediate-Release Products in Different Countries

Chairpersons: *Prof. Soji Awazu and Prof. Henning H. Blume*
Rapporteurs: *Dr. Toshihiko Kobayashi and Dr. Barbara S. Schug*
Speakers: *Dr. Roger L. Williams, Prof. Tatsuji Iga, Dr. Norman J. Pound, Dr. Tomas Salmonson, Prof. Wei Lu, Dr. Susan Walters, Prof. Suk-Jae Chung, Prof. Oliver Yoa-Pu Hu, Prof. Sompol Prakongpan, Prof. Henning H. Blume*
Panel: *Co-chairs, rapporteurs, speakers.*

Representatives of ten countries (Australia, Canada, China, Germany, Japan, Korea, Sweden, Taiwan-China, Thailand, USA) and the European Union reviewed the current status of BA (bioavailability) / BE (bioequivalence) with harmonization in mind, whilst also recognizing the need for consideration to be given to specific regional requirements that arise, for example, as a result of peculiar climatic conditions or ethnic differences. Most regulatory authorities require that these

studies should be carried out according to established guidelines for good laboratory practice with appropriate standard operating procedures. China and Taiwan-China require such studies to be carried out only in government laboratories. It was recognized that the purpose of BA / BE is to assist in ensuring the quality, safety and efficacy of all pharmaceutical products including biotech products, new active substances (NAS) and multisource products.

It was considered important that attempts be made to harmonize national/regional guidelines based on scientific principles, with flexibility to take into account specific situations in different countries (e.g. the WHO Guidelines). Considering the pharmaco-economic benefits of multisource products for patients, BA/BE studies were considered essential for the maintenance of quality equal to that required for NAS and New Drug Applications (NDA).

Appropriate guidelines should generally be implemented under conditions of good clinical practice (GCP) and ethical standards. At present, similarities between BA/BE requirements in different countries exist in terms of the use of (2×2) single-dose, crossover designs carried out in the fasted state, with an adequate washout period between phases. Biological samples, harvested according to appropriate sampling schedules are assayed by validated analytical procedures after which appropriate pharmacokinetic parameters such as AUC, C_{max} and t_{max} are calculated and analyzed with appropriate statistical methodology. Bioequivalence limits (BEL) for extent of absorption (AUC) are globally accepted. It is agreed that the acceptance standard for AUC is that the 90% confidence interval for the ratio of geometric means must meet BEL of 0.8 and 1.25. There is no agreement on acceptance standards for C_{max} or t_{max}, nor on the number of characteristics (such as gender, phenotype, patients, age) of the test subjects. The recognition and treatment of outliers remains an issue. Understanding remains to be achieved in how to ensure that batches tested in BE studies are representative of production scale lots and hence reflect final product quality.

Several issues remain to be considered at future Bio-International meetings.

- Agreement on situations in which BA or BE studies are required.
- Use of content normalization in calculating BE metrics.
- Requirements for absolute BA studies.
- Use of special populations (e.g. children, elderly, ethnic groups, patients with renal and/or hepatic impairment).
- Roles of stereoisomerism, metabolites, phenotyping in BE studies.
- Highly variable drugs.
- BE requirements for biotech products, herbal remedies.
- Use of reference to reference variability as a basis for establishment of BEL.
- Design questions such as the use of group sequential studies.
- Definition and use of international reference formulations.

Session II: Bioequivalence of Highly Variable Drugs and Drug Products: General Session, Individual Bioequivalence, and Statistical Considerations

Chairpersons: *Prof. Kamal K. Midha and Dr. Takashi Sonobe*

Rapporteurs: *Dr. Shein-Chung Chow and Dr. Kunihiro Sasahara*

Speakers: *Prof. Kamal K. Midha, Dr. Barbara S. Schug, Dr. Shein-Chung Chow, Prof. Yasuo Ohashi, Prof. Robert Schall, Dr. Lawrence J. Lesko*

Panel: *Co-chairs, rapporteurs, speakers, Dr. Rashmi Barbhaiya, Dr. Eric Ormsby, Dr. Fred Snickeris, Prof. Jun Watanabe*

It was concluded that a single set of BEL is not appropriate for all pharmacokinetic parameters (e.g. AUC and C_{max}), or for "uncomplicated" drugs and highly variable drugs/drug products. The BEL for average, population, and individual BE should be adjusted based on the intrasubject variability and the therapeutic range. BEL can be scaled according to either "internal scaling" based on estimates obtained from a replicated design or "external scaling" based on esti-

mates from previous studies. In the general discussion, it was cautioned that widening the BEL through scaling may increase the chance of two generic products being bioinequivalent with each other, even though each was itself BE with the reference product. Thus scaling would be contrary to the concept of switchability. It was also cautioned that the determination of BEL based on internal scaling may not be appropriate for two reasons: (i) The procedure could encourage the estimation of large variations which could lead to the facile declaration of BE; (ii) the estimated variations would have large uncertainties. Clearly the concept of scaling requires further consideration.

The standard 2×2 cross-over design does not provide independent estimates of intra-subject variabilities for the test and reference products, and does not permit estimation of the subject by formulation interaction term. Moreover, when there is a significant "sequence effect," it cannot be determined whether the observed effect is indeed a true sequence effect, a carryover effect, a formulation by period effect, or a chance occurrence. Replicate designs, on the other hand, do permit estimates of the intra-subject variability of the test and reference products, and the subject by formulation interaction term, and can be used to assess individual bioequivalence. The most commonly used replicate designs are either two-sequence three-period designs (e.g. RTT, TRR), or two-sequence four-period designs (e.g. RRTT, TTRR or RTTR, TRRT). The disadvantage of replicate designs is that the total exposure to the drug is not reduced, even though the number of subjects required to achieve statistical power is less than required in a standard 2×2 cross-over design for average BE studies. Moreover, since each subject is required to take the drug three or four times in a replicate design, there is a limitation on the total amount of blood that can be drawn over the time-frame of study, and the additional inconvenience of the replicate design may increase the potential for dropouts which in turn complicates statistical analysis.

Steady-state BE studies often saturate the underlying pharmacokinetics processes and thereby exhibit a dampened intra-subject variability and improved analytical precision. The controversy over extrapolation of AUC is obviated, and the BE study is carried out under conditions closer to those used in clinical practice. Steady-state BE studies may have the disadvantage that the drug may not be tolerated in healthy volunteers and that the possibility of conducting such studies in patients may be precluded by ethical or medical constraints or by virtue of complications arising from polypharmacy. It was considered that the attainment of steady-state is necessary, and that the accumulation index and differences in absorption rate may be relevant. Steady-state BE studies may be useful for those highly variable drugs and drug products that exhibit pronounced presystemic clearance.

Session III: Special Topics

Chairpersons: *Dr. Rashmi Barbhaiya and Dr. Ryoji Konishi*
Rapporteurs: *Prof. Ulf Bredberg and Prof. Tetsuya Suga*
Speakers: *Prof. Ulf Bredberg, Mr. Kanzo Kimura, Dr. Vinod p. Shah, Dr. Wallace P. Adams*
Panel: *Co-chairs, rapporteurs, speakers*

Appropriate methodologies need to be developed to cope with a variety of problems that may have impact upon BA/BE studies such as: intra-subject variability, diurnal variability, slow absorption, topical administration and long terminal half-life.

The semi-simultaneous method for the estimation of bioavailability depends on the administration of an intravenous dose followed after a short time interval (e.g. 2 h) by an oral dose, given before the first dose is eliminated. The slower the absorption, the longer the time interval required, although for a majority of drugs, a time interval of 4 h or less should be sufficient. Plasma samples are collected and the plasma concentration-time profile (the sum of the two doses) is then analyzed by non-linear regression. The method, which was validated initially by Monte Carlo simulations and then by *in vivo*

studies, offers distinct advantages over conventional methods to estimate BA. Only a single study period is required and plasma samples need only be harvested over one day. The assumption of equal clearance of the two doses is therefore more likely to be valid unless the drug is subject to very large diurnal variability in clearance. Moreover, the method is not sensitive to large extrapolated AUCs and could be very useful for drugs with long terminal half-lives. The method is less useful for sustained-release formulations or for drugs with erratic absorption profiles.

The stable isotope method has been shown to be very effective in the establishment of BA/BE for selected drugs, particularly in the context of high intra-subject variability. Most studies to date, however, have been investigational in nature. In comparison with conventional studies, the stable isotope method provides higher statistical power which in turn leads to a requirement for relatively fewer subjects. Moreover, since 1992, progress has been made in synthetic technology and in analytical methodology based on tandem mass spectrometry. Disadvantages lie in the fact that the method is not universally applicable for all drugs or formulations, the cost involved in the preparation of the analog containing a stable isotope, and the need to demonstrate that the plasma concentration time profiles of the latter are superimposable on those of the unlabeled drug, thereby showing no isotopic effect due to metabolism.

Progress has also been made in the assessment of the bioequivalence of topical preparations designed to deliver drugs to the skin to treat dermatological diseases and/or alleviate symptomology. For a product to be considered therapeutically equivalent, it must be both pharmaceutically equivalent (same active ingredient, same strength, same type of dosage form, same route of administration, and labeling comparable with that of the listed reference product) and bioequivalent to the reference product. The panel listed several different types of BE studies for topical preparations in order of preference: pharmacokinetic measurements in skin (dermatopharmacokinetic measures), pharmacodynamic measures, comparative clinical studies, and *in vitro* studies. A dermatopharmacokinetic study requires application of the test and reference products to multiple sites, each site yielding a single concentration of drug in skin. Uptake and elimination kinetics are estimated from skin samples harvested at serial times after application. The skin samples are taken by a skin stripping technique using clear adhesive tape. Preliminary studies indicate this non-invasive technique is applicable to topical corticosteroids, retinoids, antifungals and antiviral agents.

Assessment of bioequivalence using pharmacodynamic endpoints is considered appropriate for metered dose inhalants which deliver a drug topically to the lungs. The Office of Generic Drugs (US-FDA) has established a set of guidelines for pharmacodynamic study designs that emphasize the following features: (i) The selection of a relevant pharmacodynamic effect and endpoint. (ii) Documentation of dose-response. (iii) Conduct of the study in a sensitive region of the dose response curve, i.e., at 20–80% of the maximum response (E_{max} model assumed). (iv) Replicate study design. (v) "Responder" and "detector" status. A "responder" is a subject capable of showing a minimum response to the reference formulation, and a "detector" is a "responder" who is capable of showing a stated response difference between two doses of the reference product. Knowledge of the dose-response relationship is essential to ensure that the study will exhibit adequate sensitivity to detect differences between products, should such differences exist. Validation is thus essential to successful study design.