Meeting Report

Theme: Facilitating Oral Product Development and Reducing Regulatory Burden through Novel Approaches to Assess Bioavailability/Bioequivalence
Guest Editors: James Polli, Jack Cook, Barbara Davit, and Paul Dickinson

Summary Workshop Report: Facilitating Oral Product Development and Reducing Regulatory Burden Through Novel Approaches to Assess Bioavailability/Bioequivalence

James E. Polli,^{1,15} Jack A. Cook,² Barbara M. Davit,³ Paul A. Dickinson,⁴ Domenick Argenti,⁵ Nancy Barbour,⁶ Alfredo García-Arieta,⁷ Jean-Marie Geoffroy,⁸ Kerry Hartauer,⁹ Shoufeng Li,¹⁰ Amitava Mitra,¹¹ Francis X. Muller,¹² Vivek Purohit,² Manuel Sanchez-Felix,⁹ John W. Skoug,¹³ and Kin Tang¹⁴

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Abstract. This summary workshop report highlights presentations and over-arching themes from an October 2011 workshop. Discussions focused on best practices in the application of biopharmaceutics in oral drug product development and evolving bioequivalence approaches. Best practices leverage biopharmaceutic data and other drug, formulation, and patient/disease data to identify drug development challenges in yielding a successfully performing product. Quality by design and product developability paradigms were discussed. Development tools include early development strategies to identify critical absorption factors and oral absorption modeling. An ongoing theme was the desire to comprehensively and systematically assess risk of product failure *via* the quality target product profile and root cause and risk analysis. However, a parallel need is reduced timelines and fewer resources. Several presentations discussed applying Biopharmaceutics Classification System (BCS) and *in vitro*–*in vivo* correlations in development and in post-development and discussed both resource savings and best scientific practices. The workshop also focused on evolving bioequivalence approaches, with emphasis on highly variable products (HVPD), as well as specialized modified-release products. In USA, two bioequivalence approaches for HVPD are the reference-scaled average bioequivalence approach and the two-stage group-sequential design. An adaptive sequential design approach is also acceptable in Canada. In European Union, two approaches for HVPD are a two-stage design and an approach to widen C_{max} acceptance limits. For some specialized modified-release products, FDA now requests partial area under the curve. Rationale and limitations of such metrics were discussed (*e.g.*, zolpidem and methylphenidate). A common theme was the benefit of the scientific and regulatory community developing, validating, and harmonizing newer bioequivalence methodologies (*e.g.*, BCS-based waivers and HVPD trial designs).

INTRODUCTION

A 2-day workshop was held on October 22–23, 2011 in Washington, DC and focused on best practices in the

application of biopharmaceutics in oral drug product development, along with new evolving bioequivalence approaches. Entitled “Facilitating Oral Product Development and Reducing Regulatory Burden through Novel Approaches to Assess

Opinions expressed in this report are those of the authors (BMD and AGA) and do not necessarily reflect the views or policies of the FDA or AEMPS.

¹ University of Maryland School of Pharmacy, Baltimore, Maryland 21201, USA.

² Pfizer Global Research and Development, New London, Connecticut 06324, USA.

³ Food and Drug Administration, Center for Drug Evaluation, Rockville, Maryland 20857, USA.

⁴ Clinical Pharmacology and Pharmacometrics, AstraZeneca R&D, Alderley Park, Macclesfield, UK.

⁵ Janssen Pharmaceutical Research and Development, Raritan, New Jersey 08869, USA.

⁶ Bristol-Myers Squibb Company, Princeton, New Jersey 08543, USA.

⁷ Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain.

⁸ Takeda Global Research & Development Center, Deerfield, Illinois 60015, USA.

⁹ Eli Lilly and Company, Indianapolis, Indiana 46285, USA.

¹⁰ Novartis Pharmaceuticals Corporation, East Hanover, New Jersey 07936, USA.

¹¹ Merck and Company, Inc., West Point, Pennsylvania 19486, USA.

¹² GlaxoSmithKline Pharmaceuticals, Collegeville, Pennsylvania 19426, USA.

¹³ Abbott Laboratories, Abbott Park, Illinois 60064, USA.

¹⁴ Hoffmann-La Roche Inc., Nutley, New Jersey 07110, USA.

¹⁵ To whom correspondence should be addressed. (e-mail: jpolli@rx.umaryland.edu)

Bioavailability/Bioequivalence,” this workshop was co-sponsored by AAPS, FDA, and EUFEPS and featured speakers from industry, academia, and regulatory agencies. There were 154 attendees from around the world. A broad range of topics were covered, including the application of modeling in candidate selection and formulation development, *in vitro*–*in vivo* correlations (IVIVC), quality by design (QbD) implementation, and novel bioequivalence methods.

The objectives of the workshop were to:

- Provide a forum to discuss approaches to consider drug biopharmaceutic data in product development
- Discuss strategies and techniques to reduce resources expended on bioavailability/bioequivalence (BA/BE) assessments
- Review and discuss the industrial and regulatory experiences and perspectives on using the Biopharmaceutics Classification System (BCS) and IVIVC guidance for regulatory applications
- Discuss current issues in bioequivalence of oral products, including highly variable drugs and drugs needing early exposure evaluation (*e.g.*, some modified-release)
- Provide a forum to discuss formulation development case studies (*e.g.*, pediatric formulations and fixed-dose combination products)

The first day focused on drug biopharmaceutic data in product development, including the role of biopharmaceutic data in a QbD development approach. The morning of the second day focused on BCS, IVIVC, and prediction in drug development. The afternoon of the second day focused on current issues in bioequivalence of oral products. A summary of workshop presentations and themes, along with the key note presentation, are provided below. Areas for future improvements are also identified, based on speaker presentations and question-and-answer discussions.

KEYNOTE ADDRESS

Product Development and BA/BE Today

Lawrence Yu, Ph.D. (FDA) provided the keynote address. He described the objectives of a recently announced joint initiative between FDA and NIH on translational science. Through a historical overview, Dr. Yu highlighted achievements that biopharmaceutical scientists have made in this regard over the past 20 years as it pertains to oral absorption prediction, QbD and predictive dissolution, and evolving BE standards. As examples, he cited the development of cell culture system (*e.g.*, Caco-2) to estimate permeability, Lipinsky's rule of 5, the development of the BCS and Biopharmaceutics Drug Disposition and Classification System systems, biorelevant dissolution media, and models for the prediction of intestinal absorption and pharmacokinetics that are now available in commercial software packages as significant advancements that are now routine tools used in drug discovery and product development.

Dr. Yu also emphasized the important advancement of QbD in progressing the concept of enhanced product and process understanding (1). It was noted that more than 20 new drug applications (NDAs) are “QbD submissions,” and he mentioned that the Office of Generic Drugs is in the process of extending QbD to generic product development.

Dr. Yu closed with a view on future developments in biopharmaceutics that will contribute to translational science. These included advancements in cell culture models for understanding transporters and their role in oral absorption, continued advances in “e-ADME” for predicting human PK from preclinical data, the prospects for virtual BA/BE trials, and greater application of IVIVCs. He emphasized that the development of improved *in vitro* methods (*e.g.*, e-ADME, dissolution, supersaturation, and precipitation) is critical for enabling *in vivo* prediction of pharmacokinetics.

SESSION I. DRUG BIOPHARMACEUTIC DATA IN PRODUCT DEVELOPMENT

The Developability Classification System: Application of Biopharmaceutics Concepts to Formulation Development

James Butler, Ph.D. (GlaxoSmithKline) introduced the Developability Classification System (DCS) and its application to formulation development. The DCS is an adaptation of the BCS as a tool for late discovery/early development. The goal is to develop realistic formulation strategies for early development by attempting to understand what critical factors are likely to control absorption (2). Key aspects of the DCS are that BCS class II compounds (low solubility, high permeability) are further divided into solubility- and rate-limited dissolution. Classification of high/low solubility is based upon that measured in fasted simulated intestinal fluid (not the solubility minimum as per BCS); the volume to dissolve a single dose was increased from 250 to 500 ml. It was noted through several examples that BCS class IIa (*i.e.*, dissolution rate-limited class II) compounds can frequently be formulated by particle size reduction, whereas BCS class IIb (*i.e.*, solubility-limited class II) will likely require other formulation approaches (*e.g.*, lipids, amorphous dispersions). Dr. Butler closed with a perspective on the use of the DCS for predicting the likelihood of achieving an IVIVC. In his experience, IVIVCs are most likely for BCS class IIa and IV compounds, while they are unlikely for BCS class I, as gastric emptying will control absorption.

Use of Modeling Tools to Drive Efficient Product Design

Neil Mathias, Ph.D. (Bristol-Myers Squibb Company) described the use of modeling and simulation tools in product design and development. He described the advantages of modeling in that modeling facilitates the integration of physicochemical with *in vitro* and *in vivo* ADME data; it can help explain *in vivo* data; and more importantly, it guides teams to make efficient and timely decisions. The use of PBPK models, such as GastroPlus, was described (3). Typical input parameters include biorelevant dissolution, particle size distribution, precipitation time, enzyme and transporter kinetic parameters, and regional permeability values for modeling controlled release. Dr. Mathias presented several case studies illustrating the use of modeling and he

highlighted the wide range of issues that can be addressed. These include guiding formulation technology selection for poorly soluble drugs, prediction of release kinetics for the development of modified-release dosage forms, the application of virtual trials to assess the impact of polymorphic form conversion on *in vivo* product performance, and mechanistic applications such as probing food effects, reasons for delayed release, gastric emptying effects, and the potential role of transporters. It was noted that modeling tends to fail in instances where rate-limiting events extend beyond dissolution/absorption. However, such gaps and limitations are being minimized through better experimental data related to the key input parameters. It was noted that modeling approaches are gaining acceptance among clinical development groups at Bristol-Myers Squibb Company.

Empowering FIH Studies and Optimization of Drug Product Formulations

Peter Scholes, Ph.D. (Quotient Clinical) presented a lecture describing Quotient's practices in integrating clinical trial supply manufacture with the conduct of phase I pharmacokinetic studies. He described intravenous micro-tracer studies as an efficient way to obtain absolute bioavailability of a formulated product and intrinsic human pharmacokinetic properties of the compound (4). In addition, regional absorption studies have been used for many years to establish the feasibility of controlled release dosage forms. Quotient has recently implemented formulation selection studies through a process that aims to test one to several formulation prototypes directly in humans very quickly and has the benefit of being able to modify the formulation during the clinical study to achieve the desired pharmacokinetic profile. The process achieves efficiency by integrating a just-in-time GMP manufacture and immediate delivery (within 48 h) to the clinical site for dosing; in addition, formulation composition can be adjusted in real time, within the limits of the design space included in the regulatory filing, based upon pharmacokinetic data from prior legs of the phase I study. Several case studies were presented demonstrating the application to enable efficient and rapid formulation selection and optimization.

Use of Modeling to Minimize/Mitigate Relative Bioavailability Studies in Early Drug Development

John Rose, Ph.D. (Eli Lilly) described the use of modeling to minimize relative bioavailability studies in early drug development (5). Formulation changes are almost impossible to avoid during product development. A key challenge when such changes are contemplated is assessing the risk of whether *in vivo* bioavailability in humans will be significantly changed. Dr. Rose presented a three-step process for building physiologically based pharmacokinetic (PBPK) models to understand such risks and the need for relative bioavailability studies in humans. The first step is to build a computer model for the drug product and this is also the most important and difficult step. Dr. Rose emphasized that good model-building practices must be employed that consider many variables. This allows identification of critical model variables (CMV), which help define the drug product properties that are most critical for absorption (e.g., solubility,

permeability, and drug loading). Complexity increases when *in vivo* performance is strongly influenced by dose dependence and interaction of drug product with physiological conditions such as mechanical properties, fed/fasted, and GI transit times. Once a model is built, the second step involves essentially a parameter sensitivity analysis to predict the effect of CMVs on *in vivo* absorption. The third step is to simulate the test and reference drug products and compute the relative bioavailability. It was mentioned that such predictions are gaining acceptance with clinical colleagues and are being applied routinely. However, modeling findings are only one consideration in the overall decision to conduct a human relative bioavailability study or not.

TNO TIM-1 Dynamic Artificial Gastrointestinal System Role in Formulation Development and Establishing BE

Paul Dickinson, Ph.D. (AstraZeneca) described the use of an *in vitro* dissolution system, the TNO-TIM-1 system, as a surrogate for the conduct of *in vivo* studies in formulation development (6). The TIM-1 system is a dynamic dissolution system that simulates various physiological parameters in each of four compartments such as pH control, secretion of buffers (e.g., bicarbonate), mechanical mixing at each stage, transit times, and removal of solubilized drug to simulate absorption. Several examples were presented that describes how Dr. Dickinson and colleagues have applied the TIM-1 system. In one example, it was demonstrated that a BCS class II drug being used in a simple phase I formulation should be stable to precipitation at the upper doses being examined in the clinic. For that same drug, the system was utilized to provide confidence that switching from a solution to a tablet dosage form would not impact exposure.

Dr. Dickinson mentioned that tens of projects have been investigated with the TIM-1 system, with a good correlation to dog or human observed in most cases. Dr. Dickinson mentioned that his group has almost exclusively replaced formulation pharmacokinetic studies in dogs with the TIM-1 system. He suggested that, with appropriate scientific justification, the TIM-1 should be considered as a replacement for clinical BE studies where access to patient populations is difficult or healthy volunteer studies are not practical.

SESSION II. DRUG BIOPHARMACEUTIC DATA IN PRODUCT DEVELOPMENT (CONT.)

The afternoon session started with two presentations on QbD. Quality by design is a science and risk-based approach for pharmaceutical process development and manufacturing that begins with first defining clinically relevant product attributes and then designing and implementing a process to consistently deliver quality product. Thus, QbD attempts to build a process that will consistently assure the desired quality rather than the traditional method whereby subsequent testing assures quality.

When and How to Implement QbD: Industrial Perspective

Maria Cruanes, Ph.D. (Merck Research Laboratories) provided an industrial perspective that summarized the implementation of QbD at Merck where it has been adopted as a

strategic initiative (7). The QbD paradigm is applied to all compounds throughout their life cycle, starting at API selection, throughout the research and development phase, product scale-up, and continuously during production. QbD has been integrated into the company's work processes, where a scientifically driven, risk management approach clearly focuses on the delivery of quality to the patient. The integration of QbD into the work process is facilitated by standard tools to facilitate teams to follow the QbD framework. Every team is trained in the use of these tools and continuously aided by facilitators/mentors during the planning stages. The teams present the plans to management and subject matter experts for input. The tools are continuously improved based on experiences of the teams. Two tools which routinely aid with the work process are the (a) target product profile (TPP)/quality target product profile (QTPP), a tool to facilitate setting of quality requirements and (b) risk/root cause and risk analysis, a risk assessment tool. TPP/QTPP defines the product performance and quality attributes with a clear focus on the clinical outcomes. The risk assessment tool uses the quality attributes established in the TPP/QTPP tool to identify, materials, processes, and other variables that can affect these attributes. A thorough risk analysis allows defining a development/experimental plan for defining the design space and control strategy for commercialization and supply.

Development and Implementation Using QbD

Sarah Pope Miksinski, Ph.D. (FDA) discussed key aspects of QbD philosophy, with a focus on the current state of QbD implementation based on the reviews conducted by the Office of New Drug Quality Assessment of submitted QbD applications (8). One of the key tenets of the QbD is to establish a link between the process (material attributes and manufacturing process parameters), product (product quality attributes), and patient (clinical outcome). The implementation of QbD involves: (a) execution of a comprehensive risk assessment to identify material and/or process parameters that affect finished product quality, (b) understanding of multivariate interactions of process parameters and material attributes, (c) implementation of a robust control strategy to ensure consistent quality, and (d) continuous improvement to ensure that process understanding is routinely monitored and updated throughout the product life cycle. Dr. Miksinski also highlighted that a significant scientific gap in the current implementation of QbD is the integration of biopharmaceutics into product performance understanding and the setting of clinically relevant product specifications. Concrete suggestions on how the quality attributes and the clinical performance of the products may be linked using clinically relevant product specifications were provided with examples. The examples illustrated the need to gain knowledge around critical quality attributes early in formulation development.

Development and BE Experience with Fixed-Dose Combinations

Amitava Mitra, Ph.D. (Merck Research Laboratories) discussed fixed-dose combinations (FDC) of active ingredients (9). The active ingredients of these products may work through different pharmacological pathways and offer advantages of additive/synergistic effect, reduced dose of each active, and improved patient compliance. However, combining multiple active ingredients may complicate their individual

biopharmaceutical and pharmacokinetic behavior. Dr. Mitra highlighted the importance of reviewing the physicochemical and biopharmaceutical properties and their impact on pharmacokinetics of the individual drugs being considered for the FDC. Gaining a thorough understanding of the pharmacokinetic properties of the individual drugs along with the formulation variables being considered for the FDC is an equally important consideration. Pilot bioavailability studies designed to answer the most pertinent questions relating the FDC strategy are important and encouraged. However, underpowered studies with too many variables can further confound an already complex issue and should be avoided. Pivotal bioequivalence studies should be designed with due consideration of all the physicochemical, biopharmaceutic, and pharmacokinetic data for the compound from all sources. Bioequivalence study designs specific to highly variable drugs such as scaled bioequivalence or crossover replicate designs may be considered. Leveraging the knowledge gained from varying but synergistic techniques such as *in vitro* solubility/dissolution studies, *in silico* absorption models and IVIVC's, *in vivo* preclinical animal models, and the available *in vivo* clinical data is paramount to the success of the FDC strategy for a given combination. With the aid of case studies, Dr. Mitra provided examples of how the above approaches in combination can be a significant tool for the success of FDC strategies.

Stable Isotopes: a Novel Approach to PK Studies for QbD Design Space, Product Specifications, and BE Studies

Alan Parr, Ph.D. (GlaxoSmithKline) noted that developing IVIVC is desirable and is often attempted during product development. However, the development of these IVIVCs has not been as productive as anticipated. The pharmacokinetic studies necessary to develop these IVIVCs are costly, resource-intensive, and time-prohibitive. Novel approaches to relate *in vitro* data to *in vivo* performance are needed, with an emphasis in relating drug product manufacturing and quality to patient safety and efficacy. Dr. Parr discussed the application of a stable isotope approach to permit a more effective way to relate *in vitro* data to *in vivo* data (10). The approach involves conducting bioavailability studies by co-dosing subjects with the compound formulation and a small amount of enriched ^{13}C isotope-labeled compound. The enriched labeled compound serves as an internal standard and used as a covariant in the statistical analysis. This results in the reduction of variability, reducing the number of subjects required in the study and consequently the overall cost for conducting such studies. The utility of this approach was demonstrated in a dog pharmacokinetic study where this approach allowed for the reduction in intra-subject variability and demonstration of bioequivalence for the formulations evaluated. Application of this approach to human clinical studies, along with the benefits, such as the need for fewer subjects, and limitations, such as costs associated with production of labeled material, were also discussed. The application of the stable isotope approach as an aid to set product specifications, in bioequivalence studies, and evaluation of QbD design space has been discussed with relevant groups at the FDA as a proposal. The proposal was received positively by the agency and the application of the approach to a specific example was encouraged.

Strategies for *In Vivo* Studies in Product Development

Jack Cook, Ph.D. (Pfizer Inc.) stated that the objectives of pre-NDA formulation development are to determine the *in vivo* impact of key product variables to aid setting of product specifications and assess the adequacy of the formulation for its intended use. Although the objectives are easy to define, given the resource constrained environment of the industry, these objectives are not easily achieved. There is a strong desire to understand critical performance factors early in order to optimize formulations for phase III trials or marketing approval. However, over 90% of drugs entering development in humans do not make it to the market. Thus, there is a tremendous risk that resources spent early in development will be wasted as candidates attrite. Dr. Cook provided a concise presentation of the dilemma faced by the industry during formulation development and provided a data-driven approach as a solution. A Bayesian type of an approach utilizing learnings from previous data to interpret new data with a focus on using all available data was advocated over a frequentist approach where each experiment was considered in isolation. The above concept was explained using examples and suggestions that may be employed in typical development programs. The importance of thoroughly investigating and identifying the most biorelevant dissolution methodology was strongly recommended. Utilizing opportunities presented during the routine clinical development (e.g., first in man, drug–drug interaction, and early bioavailability studies) of a drug to generate data, which will be critical for defining the QbD design space, was also recommended. A distinction between the approaches that may be applied to highly soluble and lowly soluble drugs was made. Rapidly dissolving formulations are likely to ensure product performance for highly soluble drugs. For drugs with low solubility, the dissolution methods are likely to be predictive of the *in vivo* performance and a Bayesian approach to IVIVC may be considered (11).

Proposed Methods to Evaluate BA/BE in Formulation Changes of Oral Solid Dosage Forms in Drug Development in Japan

Noriyuki Muranushi, Ph.D. (Shionogi & Co.) presented on the concept of bioequivalence, stating that it was originally generated to ensure therapeutic equivalence of the generic product to the innovator product and support the post-approval changes in the innovator product to the approved drug product before the change (12). However, prior to approval of a drug, the concept of BE may not be directly applicable and a new changeability concept should be considered. Dr. Muranushi provided a description of the Japanese regulatory requirements in terms of bioequivalence as applied to post-approval changes of innovator products and for generic drugs. He also provided his personal reflections on bioequivalence and applicability of bioequivalence during development. Of note was his argument that, during development, the definition of acceptable product performance is much broader than that defined by conventional regulatory bioequivalence requirements. Hence, he proposed an alternate changeability concept, biorelevance leading to transferability, as an alternate during development, prior to the pivotal phase III trials.

The question of establishing BA/BE between various formulations used during the various development stages was specifically addressed by a working group comprised of industry representatives in the Pharmaceutical Technology Research in Quality & Technology Committee of JPMA. Dr. Muranushi outlined the main recommendation from this group was that, prior to phase III, formulations may be changed based on exposure from bridging studies comparing formulations while ensuring that drug levels do not exceed the established tolerable exposures. Conventional regulatory requirements would apply after establishment of safety and efficacy in the pivotal trials.

The Trials and Tribulations of Pediatric Formulations Development—a Clinical Pharmacologist's Point of View

Vivek Purohit, Ph.D. (Pfizer Inc.) noted that pediatric drug development presents a unique set of challenges due to the dynamic physiological changes that the population undergoes as they progress through infancy, childhood, and adolescence. The clinical development strategy adopted for pediatric development of a drug is usually dictated by the disease area, along with other clinical and regulatory considerations (13). Age-appropriate formulations such as suspensions, chewable tablets, and oral disintegrating tablets are typically developed and used in the clinical studies. However, it is not uncommon to use enabling formulations in the pivotal clinical study followed by bridging BA/BE studies. The development of age-appropriate formulations is an essential part of pediatric drug development and adds additional biopharmaceutical considerations to an already complex problem. Dr. Purohit described the unique development strategies that are typically adopted for pediatric drug development and highlighted the critical planning stages. He highlighted the importance of biopharmaceutical risk assessment as an integral part of the pediatric drug development plan. This approach was further explored using specific examples which defined the do's and don'ts of utilizing enabling formulations in pivotal pediatric trials. Bioavailability of different formulation is almost never evaluated in pediatric populations, instead relying on adult BA/BE studies. Dr. Purohit also discussed a quantitative approach utilizing population pharmacokinetic methods to determine relative bioavailability of formulations in pediatric subjects.

SESSION III. BCS, IVIVC, AND PREDICTION

FDA BCS Committee and *In Vivo* BE Studies

Mehul Mehta, Ph.D. (FDA) started his presentation by describing the FDA's BCS guidance, including what he considered to be two central concepts of this guidance (14):

1. Observed *in vivo* differences in bioavailability from two pharmaceutically equivalent solid oral products are likely due to differences in drug dissolution *in vivo*.
2. Bioavailability is unlikely to be dependent on drug dissolution and gastrointestinal transit time if the *in vivo* dissolution of an immediate-release solid oral dosage form is rapid in relation to gastric emptying and the drug has high permeability.

Thus, for rapidly dissolving products containing a BCS class I drug, *in vivo* bioequivalence is not required; bio-waivers are possible. However, Dr. Mehta stressed that initial *in vivo* bioavailability characterization is still required for NDAs. Such characterization can be obtained through mass balance and/or absolute bioavailability studies and are key data in understanding the BCS classification of a compound.

Dr. Mehta also described the CDER BCS Committee, formed in 2004, which (a) provides expert advice on all BCS review (NDA and ANDA) issues especially those where a class I claim is made; (b) serves as the point of contact for BCS-related policy, questions, interactions, and clarifications within FDA and with the external constituents; and (c) periodically evaluates if there is a need to consider updating the BCS guidance, based on internal and public information.

Composed of 11 members, the committee rules by majority; Each member may vote with options, “yes,” “no,” and “insufficient information” for BCS class I classification. The primary reviewer of the submission submits a summary package for the committee for voting consideration.

The committee has ruled on 55 drug products, in which 35 were classified as BCS class I [15 out of 28 from the new drug side and 21 out of 27 from generics side]. From the new drugs side, approximately half the cases were submitted at the IND stage and half at the NDA review stage. Six of the unsuccessful applications, from the new drug side, for BCS class I classification were due to insufficient information. Insufficient information was given as the reason for two of the unsuccessful generic side applications.

Dr. Mehta reviewed submitted permeability data and identified three points. First, for new drug applications, bioavailability data were always considered and *in vitro* methods are likely to play a supporting role. Secondly, for generic applications, *in vitro* data are more likely to be pivotal. However, there was a general unease in depending on data referenced from the literature where the committee cannot review the underlying data. Thirdly, frequently missing from submitted data are drug stability data in the gastrointestinal tract, as well as data demonstrating the suitability of the *in vitro* or *in situ* permeability method. Desirable elements include a method suitability report, use of the appropriate standard compounds, and characterization of active transporters and efflux mechanisms in the cell line.

Dr. Mehta presented case studies before considering future developments where he specifically focused on extension to BCS class III compounds. He identified promising research was being published, although the 89-fold difference in permeability over the low permeability range (*i.e.*, f_{abs} 1 to 89%) needs to be considered more carefully, with some evidence of bioequivalence issues at very low permeability.

Biowaiver Approaches for New Drug Products: Different Strengths, IVIVC, and BCS

Patrick Marroum, Ph.D. (Marroum Pharmaceutical Consulting) discussed the role of dissolution throughout the lifetime of a product, with particular emphasis on justifying product changes without the need for an *in vivo* bioequivalence study. Dr. Marroum initially discussed the case of waiver of bioequivalence studies for lower strengths of proportionally similar products, defining proportionally

similar relative to SUPAC level changes. He stated that for combination products, both components of the dosage form had to be proportionally similar to qualify for a waiver. In all cases, dissolution had to be similar. In NDAs, waiver of bioequivalence for a higher strength may be possible if the compound displayed linear kinetics, assuming proportionally similar dosage forms and similar dissolution profiles. Dr. Marroum also stated for blinded product, such as when a tablet or tablet mix is placed in a capsule, bioequivalence could be waived if no excipients are added that are known to affect bioavailability and there is comparative dissolution across the physiological pH range.

After summarizing how dissolution can be used to support SUPAC changes, Dr. Marroum then discussed dissolution/biopharmaceutics in a quality by design setting. He proposed a five-step approach to develop a dissolution method, similar to one previously described (15), with an emphasis on optimal dissolution power and adequate discrimination. He highlighted three possible outcomes:

1. No clinical data to allow dissolution performance to be linked to plasma drug levels (least optimal scenario)
2. Established range of release/dissolution characteristics resulting in bioequivalence (most applicable to immediate-release products including BCS Class I)
3. Predictive and robust *in vitro*–*in vivo* correlation (most applicable to modified-release products)

IVIVC Case Studies

Jean-Michel Cardot, Ph.D. (Université d'Auvergne) presented two case studies which yielded the conclusion that “we can trust prediction,” but only if prediction based on knowledge of the critical quality attributes and a relevant hypothesis based on API characteristics, formulation, and physiology (16). Prof. Cardot also presented data in which an IVIVC had been improved by considering the rate of drug absorption from different segments of the gastrointestinal tract.

Additionally, Prof. Cardot discussed three elements that can limit the use of IVIVC: (a) using mean or individual values; (b) correction of lag time and time scaling; and (c) flip-flop kinetics. It was observed that the frequent request from authorities to conduct individual deconvolution and then to average the results is not different from performing directly the deconvolution on the mean of the plasma concentration curve. Regarding lag time and time scaling, the presentation discussed different approaches to arrive at a lag time and/or a time scale. It was emphasized for time lag that, when lag time correction is performed, all further simulation, including predictability, must be based on a similar correction. For time scaling, it was noted that identifying a time scale factor should be justified by considering the *in vitro* dissolution method and not only simply IVIVC fitting results. Regarding flip-flop kinetics, it was advised to compare the terminal half-life extracted from the test formulations to the half-life from immediate-release or intravenous data. Flip-flop kinetics is often seen when the terminal half-life of the extended-release formulation is longer than the half-life from immediate-release or a bolus intravenous injection.

Experiences of Applying IVIVC in Projects: 1997 to Present

Colm Farrell, Ph.D. (ICON Development Solutions, LLC) considered: (a) whether pharmaceutical companies had maximized the opportunities IVIVC can bring; (b) what might prevent companies from leveraging IVIVC; (c) trends in regulatory review of IVIVC, based on his experiences; (d) progress in IVIVC data analysis; and (e) future perspectives. He briefly reviewed the 1997 guidance for industry and the approach to achieve a level A IVIVC. Dr. Farrell noted that although IVIVC could be used to predict the impact of changes to formulation and process and reduce the need for *in vivo* bioequivalence studies, there are missed opportunities (17). He was of the opinion that companies often viewed an IVIVC for post-approval changes only, rather than an opportunity to facilitate decision making during development. Hence, companies were not generating data early enough to build an IVIVC in development. This further hampered the industry as the lack of an early investigation of IVIVC may have resulted in the use of a suboptimal dissolution method. Dr. Farrell commented that for a “one-off” change, a bridging BE study could correctly be concluded as the most expedient way to move a drug project forward. However, he asked how many one-off changes do we see in practice? Dr. Farrell stated that it was more expedient to invest in IVIVC activities early in development, as this would then become the key tool to guide optimization and scale-up and also guide the development of the correct dissolution method.

Dr. Farrell described steps to ensure the development of successful IVIVC. He suggested there were two broad approaches to this: (a) optimize the dissolution method and (b) optimize the mathematical model. He thought that most IVIVC utilized a standard dissolution method (e.g., USP Apparatus 2; 50–75 rpm; pH 6.8 buffer) that could also double as a QC method and hence focused on optimizing the mathematical model. He emphasized that design of the original IVIVC study and subsequent formulation studies were important, so that external validation could be achieved and thus biowaivers gained. In his experience, using sufficient formulations in the first study to allow external validation and using the same reference formulation in subsequent studies would increase the probability of achieving external validation.

Regarding regulatory feedback, Dr. Farrell noted that grounds for rejection were often insufficient difference in the dissolution profiles (>10% needed). This issue highlighted that it was often difficult to achieve dissolution profile differences while maintaining the same release mechanism. This situation is problematic since different release mechanisms were unlikely to have the same IVIVC, and frequently, an extreme formulation (fastest or slowest dissolution) fell outside the IVIVC. The regulatory authorities were also asking for cross-validation, as well as internal validation. He inquired whether cross-validation could replace external validation. He noted that the guidance states that specification should be set to ensure the upper and lower lots were bioequivalent to the clinical formulation and did not comment that the upper and lower lots needed to be bioequivalent to each other. However, he had not seen such specifications accepted in practice. Considering the future, Dr. Farrell believed that IVIVC would have a greater role in

formulation development and technical developments would be focused on improving data analysis and modeling techniques.

Case Studies: Application of IVIVR Based on Product and Process Understanding

Yihong Qiu, Ph.D. (Abbott Laboratories) presented two case studies in which *in vitro* and *in vivo* performance had been linked. Dr. Qiu briefly discussed the guidances of the different regulatory agencies concerning degrees of product change and emphasized that degree of change needs to consider product and process understanding for the product. Dr. Qiu indicated that the dissolution test was just a physical test until the results are linked to clinical performance, which could be achieved through IVIVC (18).

The first case reviewed the utility of dissolution testing to support a change in site of manufacturing and processing for an enteric-coated product. A biowaiver was subsequently granted based on dissolution in an over-discriminatory dissolution method, relative to clinical performance. The clinical study entailed a single-dose three-way crossover clinical study investigating the performance of three different formulation variants. The biowaivers also considered a review of the manufacturing history of the product and a risk assessment considering potential failure modes that could affect clinical performance.

In the second case study, Dr. Qiu reviewed the use of an IVIVR for a fixed-dose combination extended-release tablet in which dissolution was over-discriminatory compared to *in vivo* performance. The understanding gained from the investigation allowed the specifications to be modified and harmonized in ICH countries.

IVIVC of Complex Dosage Forms

Jean-Marie Geoffroy, Ph.D. (Takeda) discussed an approach to perform IVIVC analysis on a complex extended-release oral dosage form and how such analysis was applied to propose drug release specifications (11). The formulation is a capsule containing two types of enteric-coated multi-particulate systems, to provide extended plasma levels. One type of granules releases the drug soon after entering the small intestine and contained a smaller fraction of the overall drug dose. A second type offers sustained releases and contained a larger fraction of overall drug dose. Compared to a medium or target product, fast and slow formulations were designed by modifying the amount of functional coating on the second granule type.

The FDA IVIVC Guidance was also reviewed, including how IVIVC allows for dissolution to serve as a surrogate for *in vivo* bioavailability study. The FDA IVIVC Guidance can require either internal predictability or external predictability, depending on the amount of data, therapeutic index, and range of release rates studied. For internal predictability, average percent prediction error (%PE) must be less than or equal to 10% for $C_{\max}$ and area under curve (AUC); additionally, for each formulation, %PE must be less than or equal to 15% for $C_{\max}$ and AUC.

The presentation described methods for IVIVC development, results from IVIVC, and proposed dissolution specifications. Overall, an IVIVC model was developed and internally (and externally) validated for a compound formulated as modified-release drug product. In particular, elements of the formulation design (*i.e.*, two granule population and different coating thicknesses to yield a range of dissolution profiles) were incorporated into IVIVC model approach. IVIVC analysis showed that dissolution depended on coating thickness. The IVIVC was applied to yield proposed dissolution specifications for modified-release drug product. The IVIVC model predicted dissolution profiles at the proposed high and low specifications to be equivalent to the target dissolution profile.

Use of Model-Based Simulations to Support the Paliperidone Palmitate Label

Mahesh Samtani, Ph.D. (Johnson and Johnson) discussed how model-based simulation (*i.e.*, population pharmacokinetic simulations) can be used to support product development, including in situations where bioequivalence studies are difficult to perform. In this instance, the intramuscular injectable product exhibited a half-life of 50 days, such that a small phase 1 clinical study would require 6 to 8 months.

Dr. Samtani reviewed the development history for paliperidone palmitate intramuscular injection (19). He noted that modeling and simulation were a core component to define and justify the choice of injection site, needle length, and initiation dose. These changes were required to address differences in systemic exposures observed during the phase III studies, which were run in the USA where the patients had a higher body mass index. The outcome of the modeling and simulation investigations was that an initiation dose higher than that proposed in the initial NDA filing was required. This difference was then prospectively tested in a clinical study while the FDA was reviewing the NDA. The new initiation dose was accepted by the FDA, along with a deltoid injection site and body weight-adjusted needle length for dosing. Dr. Samatani explained that the simulations were summarized in the NDA submission in a specific report called the "Dosing Document" in Module 2.5 in response to the FDA complete response letter.

Dr. Samtani also illustrated how modeling and simulation had prevented any delays to the submission and had been used to generate a dosing conversion table that allowed patients to switch from the oral paliperidone extended-release tablets directly to the intramuscular paliperidone palmitate injection.

SESSION IV. CURRENT ISSUES IN BIOEQUIVALENCE OF ORAL PRODUCTS

Current Issues in BE Evaluation in the European Union

Alfredo García-Arieta, Ph.D. (Agencia Española de Medicamentos y Productos Sanitarios) described three bioequivalence approaches currently used in the European Union (EU) (20). These approaches are (a) BCS-based

biowaivers; (b) the two-stage bioequivalence study design; and (c) widening the acceptance range for highly variable drug products. With respect to BCS biowaivers, in the EU, these are currently granted for class I (high solubility, high intestinal permeability) and class III (high solubility, low intestinal permeability) drugs. To be designated as class I or class III, the applicant must show that the highest dose of a drug substance—which was pointed out to be different than the highest dose strength, as applied in the USA—is highly soluble over the pH range of 1.2 to 6.8. Class I drug products must show rapid dissolution (>85% in 30 min) in at least three media, ranging in pH from 1 to 6.8. Class III drug products must show very rapid dissolution (>85% in 15 min) in at least three media, ranging in pH from 1 to 6.8. Standard dissolution conditions are 900 mL of media, using USP Apparatus 1 at 50 rpm or Apparatus 2 at 100 rpm. It is acceptable to use different excipients for class I drugs provided that they are not problematic (*e.g.*, with potential to affect gastrointestinal motility, interact with the drug substance, affect drug permeability, and/or interact with transporters). To receive a class III biowaiver, a generic product must contain the same excipients in very similar amounts as the corresponding reference. The EU does not grant BCS biowaivers for class II drugs (low solubility, high intestinal permeability).

To optimize the bioequivalence study design in those cases where the variability is unknown, the two-stage design has been adopted in EU, whereby a bioequivalence study can be conducted in two stages provided that the level of alpha is adjusted to obtain a coverage probability higher than 90%. The study protocol should specify both how alpha is spent and propose a sample size for the interim analysis and a minimum final sample size.

For highly variable drugs, the widening of the acceptance limits for $C_{\max}$ (not for AUC) has been finally accepted in EU. In addition, it should be justified that a larger difference in $C_{\max}$ is not clinically relevant. The $C_{\max}$ acceptance limits can be widened based on the intra-subject variability of the reference product up to 69.84% to 143.19%, which corresponds to within-subject variability of 50%. Finally, if this approach is used for $C_{\max}$, the geometric mean ratio should be constrained within 80.00% to 125.00%.

HVD: Reference-Scaled Average Bioequivalence and Sequential Design Studies

Barbara Davit, Ph.D., J.D. (FDA) discussed two approaches acceptable to the FDA for bioequivalence studies of highly variable generic drug products (21). The first is the reference-scaled average bioequivalence approach, whereby the BE acceptance limits are scaled to the variability of the reference product. An applicant planning to use this approach must specify its use *a priori* in the study protocol. Either a three-way or four-way replicated bioequivalence study design is acceptable, provided that the reference product is administered twice in order to calculate the study within-subject reference standard deviation. To use reference scaling, the within-subject standard deviation of AUC and/or $C_{\max}$ must be at least 0.294 or greater. For an acceptable bioequivalence

study, the 95% upper confidence bound of generic/reference geometric mean ratios in the study must be less than or equal to 0 (the scaled limit) and the overall study geometric mean ratio must fall within the constraint of 80–125%. The approach has been implemented successfully at the FDA's Office of Generic Drugs. To date, the FDA has granted four full approvals and one tentative approval to highly variable generic drug products which demonstrated bioequivalent to the corresponding highly variable reference products by using reference-scaled average bioequivalence.

The second approach that the FDA recommends for highly variable generic drugs is the two-stage group-sequential design. Approaches described by O'Brien-Fleming, Pocock, or Potvin are acceptable. In O'Brien-Fleming, the interim analysis alpha is conservatively small but widens with each successive look at the data. As a result, fewer study subjects may be used, but there is less likelihood that bioequivalence will be shown at the first stage. In Pocock, the same confidence interval width is used for each stage, provided that the overall alpha value is maintained at 0.05. Although this approach provides the advantage that the study can be successful at the first stage, loss of study power increases the likelihood that products may fail acceptance criteria even if bioequivalent. Potvin's method, developed by the Product Quality Research Institute and validated *via* a series of simulated bioequivalence studies, is an adaptive sequential design approach. Under Potvin, if power is greater than 80% following the first stage (at an alpha of 0.05), then the first stage becomes the pivotal bioequivalence study. If power is less than 80%, the second stage can proceed. Calculation of the number of subjects for the second stage is based on within-subject variability, and an alpha of 0.0294 if the test/reference ratio is 0.95, or an alpha of 0.0280 if the test/reference ratio is 0.90. A disadvantage of Potvin is that it is not known how to set alpha and the optimal sample size for the second stage when the test/reference ratio <0.90 because this situation has not yet been investigated in the simulation studies. FDA has evaluated inquiries and protocols presenting variations of the above three approaches. However, to date, no submission has been made for a review of a generic drug marketing application using a two-stage group-sequential design.

Add-on Studies, Sequential Design Studies, and Adaptive Design Studies

Eric Ormsby, Ph.D. (Health Canada) presented strategies to help deal with uncertainty in intra-subject variation for a bioequivalence study (22). Intra-subject variation can be reduced by treating subjects in a consistent manner for each period of the bioequivalence study, by appropriately validating the bioanalytical method used for sample analysis and by stabilizing and standardizing sample collection from the study subjects.

For highly variable generic drugs, Health Canada will accept bioequivalence studies designed using the Potvin adaptive sequential design approach, as described above. However, any bioequivalence study using a group-sequential design should maintain an overall type I error rate of 5% (alpha of 0.05), should have stopping rules based on power, and should state in the protocol exactly how the study will be executed.

Before calculating the bioequivalence statistics, the study protocol should describe how aberrant observations will be dealt with. Identification and reanalysis of individual concentrations must be described in the bioanalytical method protocol and reported in the study report. Subjects with zero concentrations for all time points should be removed from the statistical analysis. Subjects identified as extreme values may be removed if the profile meets (a) the outlier test studentized residual >3.0; (b) the profile is out of range of the other profiles; (c) all parameters used to determine bioequivalence are identified by the outlier test; and (d) no more than 5% of the subjects are considered to have extreme values. Health Canada is no longer allowing the use of add-on subjects, as applicants now have the option of using adaptive or group-sequential designs.

Measures for the Determination of Bioequivalence of Modified-release Drug Products

Laszlo Endrenyi, Ph.D. (University of Toronto) described how ideal bioequivalence metrics should exhibit the following with respect to the underlying kinetic quantity: specificity, linearity, high kinetic sensitivity, and low statistical responsiveness. AUC is linear against bioavailability (F). $C_{\max}$ reflects both F and the absorption rate constant (k_a). $C_{\max}$ is not linear against k_a but is linear against F . Kinetic sensitivity means that the metric should reflect quantitatively the underlying kinetic quantity. AUC has high kinetic sensitivity. $C_{\max}$ has low kinetic sensitivity. The test/reference $C_{\max}$ ratio varies with the test/reference k_a ratio, and the ratio of k_a/k . Therefore, changes in $C_{\max}$ are insensitive to changes in the k_a ratio.

Bioequivalence is a surrogate for therapeutic equivalence and serves as quality control to ensure the similarity of test and reference drug release profiles. Quality control calls for measures and study conditions which discriminate sensitively between features of two drug products. The single-dose bioequivalence study design is preferred for quality control because single-dose studies are the most sensitive for detecting differences. For modified-release products, single-dose $C_{\max}$ often (but not always) has higher kinetic sensitivity and better statistical responsiveness and provides better quality control (23). However, steady-state $C_{\max}$ may be clinically more important, particularly with high accumulation.

Additional bioequivalence metrics commonly used in evaluating single-dose studies include:

- $T_{\max}$ —evaluated by nonparametric comparisons, highly variable
- $C_{\max}/\text{AUC}$ —a sensitive discrimination when $C_{\max}$ and AUC are correlated
- Partial AUC (pAUC)—the AUC between two time points (*e.g.*, from time 0 to $T_{\max}$) can provide sensitive discrimination, also highly variable
- Truncated AUC—for example, from 0 to 72 h for long half-life drugs
- HVD—half-value duration, the time period during which drug concentration is within 50% of $C_{\max}$

Additional bioequivalence metrics commonly used in evaluating steady-state studies include:

- %PTF—the peak–trough fluctuation, $100 \times (C_{\max} - C_{\min}) / C_{\text{avg}}$
- %Swing— $100 \times (C_{\max} - C_{\min}) / C_{\min}$
- %AUCF— $100 \times \text{AUC above average concentration} / \text{total AUC}$
- T75%—plateau time

The FDA now requests that a pAUC be included as a metric in bioequivalence studies of modified-release methylphenidate products with complicated profiles. These formulations were developed to minimize tolerance (*via* rapid early absorption), minimize potential of drug abuse, and extend the duration of therapeutic effect. Plasma concentration profiles show an initial early rise, an approximate plateau to about 4 h, and an ascent at a more moderate rate to about 6–8 h. Either $\text{AUC}_{0-4 \text{ h}}$ or $\text{AUC}_{0-6 \text{ h}}$ can discriminate between the formulations of Metadate CD and Concerta. These two products are bioequivalent based on the usual parameters of AUC and $C_{\max}$ but show different clinical response profiles due to their different pharmacokinetic profiles. Likewise, the FDA proposes using $\text{AUC}_{0-1.5 \text{ h}}$ and $\text{AUC}_{1.5 \text{ h}-t}$ for generic versions of Ambien CR, a zolpidem extended-release tablet with a complicated profile.

In conclusion, modified-release formulations often contain either delayed- or extended-release components. It is important to recognize whether the main goal of a bioequivalence study is to serve as a therapeutic surrogate or as quality control. Metrics used for the determination of bioequivalence should have favorable characteristics such as high kinetic sensitivity and low statistical responsiveness. Additional metrics such as pAUC and HVD could be useful in determining bioequivalence of some modified-release drug products.

FDA Perspective of Applying Partial AUC Metrics

Dale Conner (FDA) described the FDA's proposal for using pAUC for some specialized modified-release dosage forms (24). The pAUC metric is useful in bioequivalence studies of multiphasic modified-release products. Such products are comprised of immediate-release and delayed- or extended-release portions, where the product is formulated to (a) achieve a rapid onset of response (b) followed by a sustained response, and (c) not accumulate to steady-state due to the dosing regimen. The examples of the zolpidem extended-release tablet (reference product Ambien CR) and the methylphenidate modified-release products (Ritalin LA, Concerta, Metadate CD) illustrate how the appropriate pAUC metrics were selected.

Ambien CR is a multiphasic product indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or maintenance. One layer releases drug content immediately, and another layer allows slower release of additional drug content. The product exhibits biphasic absorption characteristics and is given once daily, at bedtime. The most appropriate bioequivalence metrics for this product are $C_{\max}$, $\text{AUC}_{0-1.5 \text{ h}}$, $\text{AUC}_{1.5 \text{ h}-t}$, and AUC_{∞} . Clinical and pharmacodynamic data established that 90% of patients were

asleep within 1.5 h of taking a single dose of Ambien CR. $\text{AUC}_{0-1.5 \text{ h}}$ should discriminate between formulations with respect to ensuring that time of sleep onset would be the same. $\text{AUC}_{1.5 \text{ h}-t}$, to compare sustained zolpidem exposure, should ensure that sleep will be maintained in an equivalent manner for the generic and reference. As Ambien CR labeling recommends that this product be given on an empty stomach, the FDA decided to not request pAUC metrics in fed bioequivalence studies.

Ritalin LA, Concerta, and Metadate CD are different formulations of methylphenidate. All are indicated for the treatment of attention deficit hyperactivity disorder (ADHD). Like Ambien CR, each of these formulations is multiphasic, with one portion releasing drug immediately and another portion releasing drug slowly. These products exhibit biphasic absorption characteristics and are given once daily, in the morning. The bioequivalence metrics determined to be most appropriate (in fasting bioequivalence studies) are $C_{\max}$, $\text{AUC}_{0-3 \text{ h}}$, $\text{AUC}_{3 \text{ h}-t}$, and AUC_{∞} . An extensive pharmacokinetic/pharmacodynamic database on methylphenidate products established that the peak therapeutic response occurs at approximately the same time as peak methylphenidate plasma concentrations. $\text{AUC}_{0-3 \text{ h}}$ was proposed as follows: (1) mean peak drug concentrations occur at $2 \pm 0.5 \text{ h}$ post-dosing with immediate-release methylphenidate; and (2) adding 2 standard deviations ($2 \times 0.5 \text{ h} = 1 \text{ h}$) to 2 h results in a cutoff time of 3 h; which (3) should ensure that 95% of patients will have achieved the early response. Under this rationale, $\text{AUC}_{0-3 \text{ h}}$ will compare early methylphenidate exposure to ensure that two formulations will provide the same time of peak ADHD symptom control. Likewise, $\text{AUC}_{3 \text{ h}-t}$, to compare methylphenidate exposure throughout the latter part of a day, should ensure that two formulations will sustain ADHD symptom control over the same time duration. As food prolongs peak plasma drug concentrations by about 1 h when given with immediate-release methylphenidate, for fed bioequivalence studies, the optimal bioequivalence metrics are $C_{\max}$, $\text{AUC}_{0-4 \text{ h}}$, $\text{AUC}_{4 \text{ h}-t}$, and AUC_{∞} .

Limitations with Applying Partial AUC Metrics

Russell Rackley, Ph.D. (Mylan) observed that the pAUC is proposed by the FDA to ensure similarity of profiles for certain non-conventional modified-release products, considering (a) cyclic pattern of drug exposure; (b) relatively fast kinetics regarding onset/offset of action; (c) a sensitive pharmacokinetic/pharmacodynamic relationship exists; and (d) there is a pharmacological sensitivity to patterned therapy. Conventional bioequivalence measures of $C_{\max}$ and AUC are adequate for most modified-release formulations.

The questions of whether to apply pAUC metrics to bioequivalence evaluation of generic versions of complicated methylphenidate and nifedipine reference products was presented in 2010 to the Scientific Advisory Panel to Health Canada. A comparison of methylphenidate pharmacokinetics and pharmacodynamics following dosing with Metadate CD *versus* Concerta has been the subject of several articles. Metadate CD releases more drug earlier in the day than Concerta and achieves better symptom control earlier in the day. Concerta releases more drug later in the day than Metadate CD and achieves better

symptom control later in the day. By contrast, nifedipine modified-release formulations do not contain a “fast” component as a requirement for quick onset of activity. Chronic therapy with nifedipine, which does not lend to cyclical requirements, is round-the-clock. As a result, any lag differences are clinically inconsequential. In addition, plasma nifedipine concentrations extend well past the dosing interval, and pharmacokinetic/pharmacodynamic sensitivity is believed to be low. After hearing the above scientific arguments, the Scientific Advisory Panel to Health Canada concluded that the data were not compelling enough to justify special bioequivalence standards for either methylphenidate or nifedipine modified-release products.

There are limitations on assessing the pAUC requirements for zolpidem. Given the extraordinarily high variability associated with the pAUC of zolpidem extended-release tablets, it is unclear whether this metric is really a sensitive indicator. Also, the Ambien CR labeling is unclear with respect to food; the product should be given at bed time, but this may or may not be a real “fasted” state. FDA’s inferences to the “sensitive” pharmacodynamic response are not completely clear.

A number of questions should be addressed in determining whether to apply a pAUC metric to a bioequivalence study of a given product (25). For example, (a) is there a pharmacodynamic sensitivity with respect to onset/offset; (b) what is the methodology used to establish the appropriate pAUC cutoff sampling time(s); and (c) what will be the appropriate bioequivalence acceptance criteria. There is concern that the pAUC is isolated to a very small segment of the concentration–time profile, with potential to dramatically inflate variability. The generic industry cannot always anticipate the agency’s interpretation, despite the application of “good science,” and would appreciate the presentation of good case studies, with a full summary basis of rationale. Perhaps a forum, to include the industry and academia, could be organized to lead to an objective and systematic approach to validate this metric.

AREAS FOR FUTURE IMPROVEMENTS

A common theme in many panel discussions was the lack of consistency of acceptable regulatory practices across regions (26). For example, some regulatory agencies allow scaling in the analysis of *in vivo* bioequivalence trials and others do not. Similarly, some regulatory agencies allow dissolution-based waivers for BCS class III drugs while others do not. Some do not allow BCS-based waivers for any drug. The ultimate consequence of this lack of harmonization is that global companies are forced to resort to a bioequivalence methodology that is acceptable to all regulatory bodies where the product will be submitted. This situation typically results in the necessity to perform two-way crossover studies, even when the drug is BCS class I or whether it is highly variable. It was generally recognized that this practice is generally the most costly in terms of both time and resources and may put healthy volunteers unnecessarily at risk. A common theme was a benefit if the scientific and regulatory community could harmonize on newer bioequivalence methodologies (e.g., BCS-based waivers and *in vivo* trial designs for highly variable drugs).

An additional theme that was discussed extensively was the application of modeling during discovery and development to establish critical product attributes (27). These parameters were being used to help implement QbD and design product to improve clinical efficacy and safety or reduce patient variance that results in cost saving by reducing the clinical studies size. To fully exploit modeling, further collaboration is required across industry, academia, and the regulators to validate *in vitro* models that are required by the models (e.g., supersaturation, gastrointestinal motility, regional absorption differences within the gastrointestinal tract). For example, current models are typically based on a surprising limited amount of human permeability data. It would be of mutual benefit to all to further expand our knowledge in these areas. Finally, we require tools to help us differentiate between variables that we can control *via* product attributes *versus* variables that are biological in nature and have no control over (28).

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