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MINI REVIEW

Regulatory utility of mechanistic modeling to support alternative bioequivalence approaches: A workshop overview

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Abstract

On September 30 and October 1, 2021, the US Food and Drug Administration (FDA) and the Center for Research on Complex Generics cosponsored a live virtual workshop titled "Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches." The overall aims of the workshop included (i) engaging the generic drug industry and other involved stakeholders regarding how mechanistic modeling and simulation can support their product development and regulatory submissions; (ii) sharing the current state of mechanistic modeling for bioequivalence (BE) assessment through case studies; (iii) establishing a consensus on best practices for using mechanistic modeling approaches, such as physiologically based pharmacokinetic modeling and computational fluid dynamics modeling, for BE assessment; and (iv) introducing the concept of a Model Master File to improve model sharing between model developers, industry, and the FDA. More than 1500 people registered for the workshop. Based on a postworkshop survey, the majority of participants reported that their fundamental scientific understanding of mechanistic models was enhanced, there was greater consensus on model validation and verification, and regulatory expectations for mechanistic modeling submitted in abbreviated new drug applications were clarified by the workshop.

Andrew Babiskin and Fang Wu contributed equally to this study.

In the area of pharmacology and biopharmaceutics, mechanistic models are built on basic chemical, physical, and biological/physiological principles to describe all relevant processes that a drug product undergoes once administered to humans or preclinical species or when tested in an in vitro system. These processes include metamorphosis of the dosage form and release of the active ingredient from the drug product as well as drug absorption, distribution, metabolism, and excretion and downstream pharmacodynamic effects. These mechanistic models are integrative systems that aim to predict the drug exposure (both systemically in the blood and in a specific tissue) and to provide information relevant to the safety and efficacy of the product based on the physicochemical properties of the active ingredient, the formulation characteristics of the drug product, and the interaction of the active ingredient and the formulation with the physiological system.

One such mechanistic modeling approach is physiologically based pharmacokinetic (PBPK) modeling, which traditionally is a compartmental-based modeling approach that integrates in vitro information (e.g., in vitro dissolution and particle size distribution) with physicochemical properties of the active ingredient and physiological factors to predict the systemic and local exposure of the active ingredient in different tissues. For applications relating to bioequivalence (BE), the mechanistic absorption components of the models have generally been the focus because these describe formulation differences in the model.[1] Another mechanistic modeling approach with applications in the area of pharmacology and biopharmaceutics is computational fluid dynamics (CFD). CFD is a physics-based modeling approach for tracking fluid and particle transport in relevant, biorealistic geometries. For example, CFD can be used to track the fate (i.e., the site of deposition) of individual aerosols emitted by inhalation devices and determine the movement of a solid dosage form and its metamorphosis as it travels through the contours and stress of the gastrointestinal (GI) tract.[2,3]

Mechanistic models, particularly PBPK models, have successfully been used in regulatory submissions to support new drug and generic drug product development and approval. Specific areas of application include drug–drug interaction,[4–6] biowaiver,[7,8] in vitro–in vivo correlation,[8] risk assessment,[8–10] clinically relevant specification setting,[8–12] and BE.[12–14] As the prevalence of PBPK modeling in regulatory submissions increases, some common challenges have arisen related to implementing applications of PBPK modeling for BE assessment. These have included challenges related to what would constitute suitable model validation (e.g., a recognized standard for acceptable model performance), the generation and use of in vitro characterization data (e.g., dissolution or in vitro release test data) that can be biorelevant/biopredictive, and the assessment of relevant in vivo data sets for model development and verification and validation. It is imperative that we address these challenges associated with model development and application because for certain drug products, PBPK models may represent the most promising way to overcome barriers currently limiting the development and assessment of BE for oral and locally acting drug products. For example, to develop model-based evidence to potentially support waiving fed in vivo BE studies for oral drug products, we need to address challenges related to developing a PBPK model under fed conditions that adequately describes the interaction between food, GI physiology (e.g., GI motility), and the active ingredient and the formulation.[15,16] Similarly, for locally acting drug products, we need to address challenges related to quantifying the amount of an active ingredient at or near the putative site of action.[17,18] Such models may need to be informed by drug product quality and performance attributes as well as human physiology.

The US Food and Drug Administration's (FDA's) Office of Generic Drugs (OGD) has historically used mechanistic modeling and simulation to support regulatory decision making and has directly supported the development of modeling platforms through Generic Drug User Fee Amendments (GDUFA) research funding.[19] The scientists in the OGD often use these tools to support regulatory decisions related to BE issues, including the assessment of abbreviated new drug applications (ANDAs), pre-ANDA development meetings, citizen petition responses, controlled correspondences, and product-specific guidances (PSGs).[20,21] The generic drug industry has also used mechanistic modeling within their ANDAs to address issues related to BE either (1) in support of novel BE approaches as an alternative to traditional or PSG-recommended approaches[22,23] or (2) to address complex review issues that arise after performing the recommended BE studies.[21]

The Center for Research on Complex Generics (CRCG), a collaboration between the University of Maryland School of Pharmacy and the University of Michigan College of Pharmacy that was established through an FDA grant dedicated to addressing scientific challenges/needs related to complex generic drug development, has recently conducted a survey titled "Survey of Scientific Challenges in the Development of Complex Generics."[24] In this survey, generic industry members were queried to determine the areas of research where GDUFA science and research efforts should be prioritized. In their responses to the survey, about 50% of respondents identified locally acting PBPK modeling as a crucial method of analysis where additional effort is needed toward the development of a locally acting drug product. Specifically, the interest in PBPK modeling for locally acting products, which are

generally considered complex drug products (with some exceptions), tended to be in support of BE approaches that would represent alternatives to conducting comparative clinical end-point BE studies in patients, in support of BE studies with pharmacokinetics (PK) endpoints, or to expand the use of in vitro characterization-based BE approaches (e.g., to expand the eligibility of products with minor differences in formulation composition compared with a reference standard product). The next largest proportion (more than one third of respondents) identified "oral absorption models and BE" (i.e., oral PBPK) as a crucial method of analysis. Although the majority of oral generic drug products are not identified as complex generics due to widely recognized and established PK BE study recommendations, oral products represent a significant portion of innovator and generic products, and both the FDA and generic industry respondents expressed interest in further streamlining drug product development with a reduced use of human in vivo studies.

Appreciating this common goal and the collective need to enhance the development of PBPK and CFD models for regulatory use, the FDA, CRCG, and industry collaborated on the development of a 2-day workshop cosponsored by the FDA and the CRCG to advance applications of mechanistic modeling for the purposes of determining BE and addressing other related issues for generic drug products. The main aims of the workshop were to:

1. Engage the generic drug industry and other involved stakeholders regarding how mechanistic modeling and simulation can support their product development and regulatory submissions
2. Share the current state of mechanistic modeling for BE assessment through case studies
3. Establish a consensus on best practices for using PBPK and CFD modeling for BE assessment to help drive further investment by the generic drug industry into mechanistic modeling and simulation
4. Introduce the concept of a Model Master File to improve model sharing between model developers, industry, and the FDA

The workshop was organized in three symposia (Table 1). Symposium 1 included three sessions focusing on specific locally acting drug product categories and the utility of mechanistic modeling for those categories. Symposium 2 included three sessions focusing on different application areas for PBPK modeling for oral drug products, the challenges, and successful case studies. More detailed descriptions of the proceedings will be published separately for each session of the Workshop in the context of locally acting drug products and oral drug products. Symposium 3 contemplated future directions, introducing a novel concept for a Model Master File that could facilitate efficient model sharing between model developers, product developers, and FDA regulators. This closing symposium of the workshop included only a single session focusing on the broader concept of model acceptance and sharing for regulatory use and was more exploratory in nature than Symposia 1 and 2 (which are the main focus of this workshop overview). Each session included presentations followed by a panel discussion. More than 1500 people had registered for the workshop, and approximately 700 people attended these sessions on the day of the workshop. For those who were unable to attend these sessions on the day of the workshop, all presentation files and session video recordings were made available on the CRCG website at https://complexgenerics.org/PBPK2021/.

TABLE 1 Workshop symposiums and sessions

	Day 1: September 30, 2021	**Summary citation**
Symposium I	Mechanistic Modeling of Locally Acting Generic Drug Products	
Day 1: Session 1	Mechanistic Modeling of Orally Inhaled Generic Drug Products	[25]
Day 1: Session 2	Mechanistic Modeling of Dermal Generic Drug Products	[26]
Day 1: Session 3	Mechanistic Modeling of Other Locally Acting Generic Drug Products	[27]
	Day 2 October 1, 2021	
Symposium II	Mechanistic Modeling of Oral Generic Drug Products	
Day 2: Session 1	Oral PBPK as an Alternative BE Approach and a Tool for Supporting Risk Assessment and Biowaiver	[28]
Day 2: Session 2	Oral PBPK for Evaluating the Impact of Food on BE	[29]
Day 2: Session 3	Challenges and Successful Cases for Oral PBPK	[28]
Symposium III Day 2: Session 4	Model Acceptance and Model Sharing for Regulatory Use	

Abbreviations: BE, bioequivalence; PBPK, physiologically based pharmacokinetic.

A survey of those who registered for the workshop (conducted after completion of the workshop) indicated that for the majority of workshop participants, (1) the locally acting and oral PBPK sessions during the workshop had enhanced their fundamental scientific understanding of mechanistic models, (2) they had gained more consensus on model validation and verification, and (3) they had learned more about regulatory expectations for mechanistic modeling submitted in ANDAs. As such, this workshop substantially enhanced the communication and alignment of understanding between industry, academia, and the FDA on these topics and resulted in some consensus on using mechanistic modeling to assess BE or relative bioavailability during drug product development.

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CONFLICT OF INTEREST

The opinions expressed in the article are those of the authors and should not be interpreted as the position of their organizations/employers. The opinions expressed in the article are those of the authors and should not be interpreted as the position of the US Food and Drug Administration. The authors declared no competing interests for this work.

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