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PERSPECTIVE

Mechanistic Oral Absorption Modeling and Simulation for Formulation Development and Bioequivalence Evaluation: Report of an FDA Public Workshop

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On May 19, 2016, the US Food and Drug Administration (FDA) hosted a public workshop, entitled "Mechanistic Oral Absorption Modeling and Simulation for Formulation Development and Bioequivalence Evaluation."[1] The topic of mechanistic oral absorption modeling, which is one of the major applications of physiologically based pharmacokinetic (PBPK) modeling and simulation, focuses on predicting oral absorption by mechanistically integrating gastrointestinal transit, dissolution, and permeation processes, incorporating systems, active pharmaceutical ingredient (API), and the drug product information, into a systemic mathematical whole-body framework.[2]
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Dr. Kathleen Uhl, Director of the Office of Generic Drugs (OGD), opened the discussion. In her opening remarks, Dr. Uhl highlighted the potential impact and benefits of implementing the innovative tool of mechanism-based modeling and simulation in the context of generic drug product development and review for both industry and the regulatory agency. With all these efforts, mechanism-based modeling and simulation can potentially improve the first cycle approval rate of generic drug products and further accelerate public access to generic products.

Dr. Liang Zhao (FDA, workshop chair), indicated areas where modeling and simulation practices have been employed for both generic and new drugs in the regulatory setting. Specifically, in the generic drug program, internal efforts utilizing modeling and simulation to inform regulatory decision making are significant.[1] Although oral absorption modeling has been used intensively within OGD, there is currently a lack of modeling and simulation reports in Abbreviated New Drug Applications (ANDAs) submissions. Dr. Zhao also highlighted the Physiologically Based Pharmacokinetic (PBPK) reviews in New Drug Applications (NDAs) including the numbers and impacts on product labels. At the end, Dr. Zhao concluded his introduction by emphasizing the areas where mechanism-based absorption models can have high impact.

PLENARY AND PANEL DISCUSSION SESSIONS

Dr. John Duan and Dr. Xinyuan Zhang, both from the FDA, shared their experience in utilizing physiologically based absorption modeling in new drug and generic drug regulatory activities, respectively. Dr. Duan's presentation first set the stage for the application of mechanistic oral absorption modeling in biopharmaceutics review by focusing on the concept of "patient-centric quality" and the "bridging" role of "biopharmaceutics" in product development, approval, and product lifecycle management. Although absorption modeling and simulation (M&S) currently only accounts for a small portion of total PBPK modeling submissions, it has great potential in biopharmaceutics applications. Three examples were enumerated where absorption M&S was applied to select a clinically meaningful dissolution test method, to define the dissolution and particle size specifications, and to understand the impact of quality attributes on product performance by performing multidimensional parameter sensitivity analysis (**Table 1**). In addition, common limitations in regulatory submissions regarding mechanistic oral absorption models and simulations were indicated, such as model exercises that were performed but not fully utilized in submission; detailed information was not provided; model was not fully verified; model files were not provided; rationale was not clear; and justifications were not reasonable. Based on these, Dr. Duan listed the necessary elements for mechanistic oral absorption models in regulatory submissions including detailed model information (input parameters, optimized parameters, software type and version, logical description of model building and validation process, executable model files, and simulation conditions), appropriate justifications for input parameters (sources and selection, optimized parameters, raw data to support the model verification and correlation), and rationale to support the request for regulatory actions. Dr. Duan concluded his presentation by a forward-looking view to meet the challenge in drug development.

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Table 1 Summary of case examples using absorption modeling and simulation in each presentation

Representative	Case examples of absorption modeling applications
Biopharm/Office of Pharmaceutical Quality	• Identify clinically relevant dissolution method (pH 2 vs. pH 6.8) for an immediate-release (IR) product • Define dissolution and particle size distribution specifications for a delayed-release enteric coated product • Explore the impact of uncertainty in estimated parameters on model predictions and parameters of interest using multidimensional sensitivity analyses
OGD	• Investigate the impact of slower drug release from the drug product in acidic media and the change in a critical product attribute on warfarin pharmacokinetics (PK) • Evaluate the impact of proton pump inhibitors (PPIs) on bioequivalence (BE) of generic prasugrel HCl tablets and fingolimod capsules to their brand name products
Innovator company	• Guide development of a formulation that produces target exposure and is less sensitive to the change in stomach pH • Investigate the dissolution impact on PK and BE for enteric-coated beads of a BCS Class 1 compound • Identify clinically relevant dissolution method (pH 2 vs. pH 4.5 and 6.8) for a BCS Class 2 weak base compound • Assess potential risks from salt to base conversion as a function of stomach pH for a weak base BCS Class 2 drug • Predict food effect for a weak base BCS Class 1 drug • Predict PK of new formulations for a BCS Class 2 drug using absorption modeling based IVIVC and incorporating regional dependent absorption
Generic company	• Characterize the reference listed drug (RLD) and design generic product development strategy for a BCS Class 4 drug • Identify bio-indicative dissolution test conditions and clinically relevant specification limits for a BCS Class 1 extended-release (ER) product • Justify waiver of *in vivo* studies for intermediate strengths using level A IVIVC • Define the boundaries for release rate controlling polymers based on bio-indicative dissolution method identified using absorption modeling
Academia	• Impact of motility phase dependent gastric emptying and its variation on PK profiles and BE trials (cimetidine, and viral compounds) • Impact of *in vitro* dissolution on PK prediction (*in vivo* predictive dissolution)
Tool developer – Simcyp	• Explore the impact of *in vitro* dissolution fitting methods, optimization and weighting schemes, gastric emptying, and factoring population variability on mechanistic IVIVC model predictions/development of metoprolol ER formulations and predict their PK in CYP2D6 poor metabolizers • Determine dissolution specifications for a tramadol ER formulation • Assess therapeutic equivalence for ibuprofen IR products using absorption/PBPK/pharmacodynamic (PD) modeling • Extrapolate formulation assessment from adult to pediatric populations • Predict and understand food effects for multiple compounds
Tool developer – SimulationsPlus	• Develop IVIVCs to predict PK for BCS Class 1 ER products, risperidone (BCS Class 2) IR tablets • Develop virtual BE trials to establish dissolution specification • Understand food effect using oral absorption modeling • Assess the effect of particle size on API exposure for an IR formulation for which a biowaiver request was granted
Tool developer – PK-Sim	• Integrate *in vitro* dissolution data to predict PK for various dosage forms • Identify the source of variability for diclofenac enteric-coated tablets and furosemide tablets • Predict the influence of the particle size on the rate and extent of absorption for cilostazol under both fasted and fed conditions in dogs • Predict food effect for a test drug IR tablets, regional absorption for its granules, and PK for its controlled-release gastrointestinal therapeutic system formulation • Predict grapefruit juice-induced food–drug interaction for nifidepine IR formulations • Predict indomethacin exposure after oral administration in preterm neonates
OrBiTo	• Predict active pharmaceutical ingredient (API) dissolution based on particle size distribution (PSD) • Predict first in human (FIH) PK based on API PSD • Incorporate *in vitro* dissolution profiles in the model to define API PSD specifications

Subsequently, Dr. Zhang provided an update on the regulatory activities based on absorption M&S in OGD with two case examples, and an update on the Generic Drug User Fee Amendments (GDUFA) research efforts to modernize the toolset of oral absorption M&S. In the past decade, absorption M&S tools have been used actively to address a wide range of scientific questions in OGD.[2–7] One example presented was the evaluation of the impact of slow dissolution in a specific pH condition on bioequivalence (BE) for warfarin sodium tablets. In this example, a human BE study was conducted to confirm the model prediction and the model prospectively predicted the *in vivo* BE outcome. However, not every simulation can be confirmed by an *in vivo* study. In this case, communicating the results and conclusions to nonmodelers in a way that could have informed a decision that the *in vivo* study was not needed, and not the modeling task itself, was challenging. Accumulating positive predictive experience on absorption modeling can help communicate the value of proactive modeling to pharmaceutical decision making. The second case example involved investigating the impact of proton pump inhibitors (PPIs) on BE for prasugrel HCl tablets and fingolimod capsules (**Table 1**). Both examples helped define product quality specifications. Dr. Zhang concluded that there are existing challenges in predicting oral absorption. Therefore, further research efforts and scientific studies including GDUFA-funded research are needed to advance and sharpen the relevant toolsets.

Dr. Filippos Kesisoglou (Merck), and Dr. Jasmina Novakovic (Apotex) presented applications of absorption modeling and simulation from the new drug and generic drug industry perspectives, respectively. Dr. Kesisoglou provided six case examples (**Table 1**) covering a wide range of applications in new drug development, including guiding early formulation development, projection of BE outcomes, impact of the API form on bioavailability, food effect projection, and development of mechanism-based *in vitro*/*in vivo* correlations (IVIVCs).[8] In Dr. Novakovic's presentation, multiple stages in the generic drug development and life-cycle management were illustrated where PBPK absorption modeling plays a pivotal role for the reference product characterization, quality target product profile establishment, formulation design and product development, defining bio-indicative dissolution test conditions, and clinically meaningful specification limits. She provided a case example where PBPK absorption modeling was used to refine a formulation development strategy (**Table 1**).

The morning session concluded with Dr. Gordon Amidon (University of Michigan), the inventor of the Biopharmaceutics Classification System (BCS). He emphasized that the key to accurate predictions is model input. He pointed out that our current dissolution methodology, e.g., USP methods, is a quality control methodology. Further, our biorelevant dissolution media are only approximate. He emphasized that we need more directly measured human physiological variables, including mean, median, and statistical ranges and probability distribution or density function to model truly predictive *in vivo* absorption. Such *in vivo* measurements need to be performed under typical dosing conditions, fasted and fed, and BE trial conditions and an *in vitro* dissolution methodology needs to incorporate those physiological variable ranges. He noted that BCS class and the recently proposed subclasses,[9] e.g., acid, base, neutral, is a starting point for developing a predictive dissolution methodology. Finally, he noted that a predictive dissolution methodology would be an extremely valuable tool for a formulation scientist in developing an oral drug product and would be very useful in determining critical variables for quality by design (QbD) and process analytical technology (PAT) purposes.

The afternoon session consisted of three presentations from software developers: Dr. Masoud Jamei (Simcyp), Dr. Viera Lukacova (SimulationsPlus), and Dr. Thomas Eissing (Bayer), and one presentation from OrBiTo (by Dr. Filippos Kesisoglou). Echoing Dr. Amidon's talk, all three presenters (Dr. Jamei, Dr. Lukacova, and Dr. Eissing) provided case examples utilizing PBPK absorption models to link *in vitro* dissolution with *in vivo* performance and again exemplified the importance of getting *in vivo* predictive *in vitro* dissolution as the appropriate model input (**Table 1**). Modeling of *in vitro* dissolution experiments was also

Table 2 Summary of panel questions and discussions

Questions	Discussions
In which areas do we have the highest confidence in using PBPK absorption modeling?	• Solubility (vs. pH) profile, particle size, and *in vitro* dissolution are three parameters that have been presented in multiple examples from the presentations. • Parameter sensitivity analysis is a commonly used procedure in model assessment and application to allow us increasing confidence on well-described parameters. Yet the interplay or correlation between parameters should be taken into consideration. • Different opinions were expressed on the level of confidence in prediction of food effect and proton pump inhibitor (PPI) effects on absorption. Although the prediction accuracy was not always satisfactory, there were successful case examples of food effect and PPI effect prediction in the literature, which should not be discounted. • PBPK modeling is a very resource-intensive process, and, therefore, should be reserved for high-risk products. However, it was indicated that models helped understand and explain to formulation groups and clinical colleagues mechanistically and explicitly product performance of low-risk drug products.
Do we have enough experience and confidence in applying PBPK absorption models to support regulatory applications?	• For specific cases, the panel agreed that PBPK absorption modeling can help understand what the risks are when widening the BCS Class 3 biowaiver criteria (such as proposed longer dissolution time than very rapidly dissolve and/or different excipients). • On to the level of confidence in each area, the panel members agreed that it has to be examined on a case-by-case basis and no general conclusions can be drawn at the moment. • Another question triggered by the aforementioned discussion was how much model and extrapolative step qualification is needed to give scientists enough confidence to trust the model prediction. This question remained open to further discussion after the workshop.
What are the gaps in the prediction and how to close them through research?	• Besides the gaps in scientific understanding, there is also a confidence gap in what people believe in PBPK model prediction and what our assessment of the model is. • Scientific gaps identified included excipient effects, biopharmaceutics knowledge, and/or biorelevant dissolution methodology on a compound/product basis, the lack of *in vivo* data on the dissolution of drug products in the gastrointestinal (GI) tract, and local permeability in the GI tract. • Publishing and developing databases and repositories were suggested as ways to share the knowledge acquired by stakeholders involved in the PBPK model development process.

mentioned as a tool to improve *in vivo* translation. Physiologically based IVIVC was discussed in all three presentations with the message that the key advantage, compared to conventional IVIVC, is that the deconvoluted input profile is the predicted *in vivo* dissolution, and not the absorption fraction, which is often confounded by dissolution, permeability, and gut metabolism processes. Dr. Jamei advocated incorporating physiologically realistic fluid dynamics and luminal fluid volumes into absorption models. Finally, he discussed the opportunities and challenges including knowledge gaps in systems data and absorption mechanisms, inter-occasion variability, colonic absorption, and education. Dr. Lukacova followed with a case where the postapproval process change resulted in different particle size distributions for the new lots for a specific drug product. Waiver of an *in vivo* study was granted based on PBPK absorption modeling, parameter sensitivity analysis for the particle size distribution, and virtual BE simulations. Dr. Eissing provided several case examples where PBPK absorption modeling has been successfully used to bridge *in vitro* particle size distribution or dissolution with *in vivo* performance, characterize PK variability, food effect prediction, and regional absorption prediction. Finally, Dr. Eissing introduced population PBPK where variability and uncertainties of PBPK parameters and predictions could be assessed given model structure, prior knowledge, and combining intravenous (i.v.) and per os (p.o.) datasets. He also argued for full transparency of models including structure and parameterization for general physiology as well as specific application to allow for a rigorous scientific assessment.

The OrBiTo project vision is to "transform our ability to accurately predict the *in vivo* performance of oral drug products across all stages of drug development." Dr. Filippos Kesisoglou, on behalf of OrBiTo, gave an overview of the mission, vision, and the most recent achievements of the project. Two examples (**Table 1**) were presented to highlight the urgent need of identifying *in vivo* predictive/biorelevant dissolution testing in establishing a connection between drug dissolution and clinical performance.

The panel members consisted of speakers and internal FDA experts. The questions and major discussion points are summarized in **Table 2.** Briefly, many successful cases were presented in each presentation. The most frequently presented applications were to define quality-related product specification (such as particle size distribution and *in vitro* dissolution). Food effect prediction, mechanistic IVIVC, and drug–drug interactions associated with gastric pH modifications were also of significant interest due to the potential of reducing unnecessary studies in development, and facilitating biowaiver granting. However, the confidence levels in each area have to be evaluated on a case-by-case basis.

CONCLUSION

Productive discussion was generated around the questions (**Table 2**), and the panelists expressed different opinions in response to the questions, such as the level of confidence in prediction of food effect and PPI effects on absorption. The panel members also reached consensus regarding the level of confidence in each area that has to be examined on a case-by-case basis and no general conclusions can be drawn at the moment.

In the closing remarks, Dr. Robert Lionberger (OGD) emphasized that mechanism-based oral absorption M&S is a critical core technology area for the generic drug review function at the FDA, but is also a knowledge gap for OGD. There is broad interest across the Center for Drug Evaluation and Research and the FDA in continuously advancing these tools.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLAIMER

The views expressed in this article are those of the authors and not necessarily those of the Food and Drug Administration (FDA).

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