The AAPS Journal (2024) 26:19
https://doi.org/10.1208/s12248-024-00886-x

REVIEW ARTICLE

Best Practices for Utilizing Modeling Approaches to Support Generic Product Development: A Series of Workshop Summary Reports

Using Mechanistic Modeling Approaches to Support Bioequivalence Assessments for Oral Products

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Received: 30 September 2023 / Accepted: 20 December 2023 / Published online: 24 January 2024

Abstract
This report summarizes the proceedings for Day 1 Session 3 of the 2-day public workshop entitled "Best Practices for Utilizing Modeling Approaches to Support Generic Product Development," a jointly sponsored workshop by the US Food and Drug Administration (FDA) and the Center for Research on Complex Generics (CRCG) in the year 2022. The aims of this workshop were to discuss how to modernize approaches for efficiently demonstrating bioequivalence (BE), to establish their role in modern paradigms of generic drug development, and to explore and develop best practices for the use of modeling and simulation approaches in regulatory submissions and approval. The theme of this session is mechanistic modeling approaches supporting BE assessments for oral drug products. As a summary, with more successful cases of PBPK absorption modeling being developed and shared, the general strategies/frameworks on using PBPK for oral products are being formed; this will help further evolvement of this area. In addition, the early communications between the industry and the agency through appropriate pathways (e.g., pre-abbreviated new drug applications (pre-ANDA) meetings) are encouraged, and this will speed up the successful development and utility of PBPK modeling for oral products.

Keywords absorption · mechanistic modeling · oral products · virtual bioequivalence

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Introduction

The US Food and Drug Administration (FDA) and the Center for Research on Complex Generics (CRCG) held the workshop titled "Best Practices for Utilizing Modeling Approaches to Support Generic Product Development" on October 27–28, 2022. The purpose of this workshop was to discuss modernization approaches to efficiently demonstrate BE, establish their role in modern paradigms of generic drug development, and explore and develop best practices for the use of modeling and simulation approaches in regulatory submissions and approval.

Day 1 Session 3 of this workshop focused on using mechanistic modeling approaches to support BE assessments for oral products using physiologically based pharmacokinetic (PBPK) absorption modeling. Speakers from Session 3 presented on using PBPK absorption modeling to support risk assessment from regulatory and industry perspectives, waiver of fed BE studies, establish BE for pediatric drug products, and establish BE safe space using dissolution data

for oral solid dosage forms. A thorough panel discussion followed these presentations in which the panel members highlighted several technical and regulatory key aspects regarding PBPK absorption model development and applications.

Presentations

The major points of the four presentations and panel discussions included in this session are summarized.

> Summary of Presentation "Using PBPK Model to Support Risk Assessment for Oral Products, from a Regulatory Perspective" by Fang Wu, Senior Pharmacologist and Scientific Lead from the Office of Research and Standards (ORS), Office of Generic Drugs (OGD), Center for Drug Evaluation and Research (CDER), US FDA[1]

Briefly, Dr. Wu presented the regulatory questions that PBPK absorption modeling can help answer in generic drug development in recent years, including two research highlights, using PBPK absorption modeling to evaluate food impact on BE and evaluate the impact of gastric pH on BE. Dr. Wu discussed a collaborative research that investigated 170 drugs with clinical food effect from the literature and new drugs approved by the US FDA from Year 2013 to 2019 (1). The project found that drugs with significantly positive food effect were BCS Class II or IV, whereas drugs with significantly negative food effect were Biopharmaceutics Classification System (BCS) Class I or III. While assigning confidence based on BCS classification may be over-simplified, this high-level categorization helps for initial risk assessment. Findings also showed that food effects on orally administered drugs are mediated by the gastric emptying and gastrointestinal (GI) pH. Generally, PBPK absorption models may predict the food effect better for the molecules where the food effect is arising from simple mechanisms such as solubility or dissolution enhancement as compared to those involving complex mechanisms, such as transporter, metabolism, food-drug complex formation, and formulation-mediated food effect. On that account, relevant research is needed to understand the above mechanisms including the formulation-mediated food effect. Dr. Wu also presented findings from an internal research that utilized PBPK absorption modeling to assess the impact of food intake and excipients on the BE of generic acyclovir immediate release (IR) tablet using virtual healthy subjects and virtual bioequivalence (VBE) trials, as a proof of concept study. VBE conducted under both fasted and fed conditions indicated food appears not to impact the BE results for the acyclovir IR tablet. Dr. Wu also introduced a regulatory case example, using PBPK absorption modeling to evaluate the food impact on BE for oral tablets containing an active pharmaceutical ingredients (API) as amorphous solid dispersion form. Based on the risk and complexity of the formulation of the proposed product, the major concerns/limitations of the developed PBPK absorption model were identified. These concerns include the lack of supporting information related to formulation design, manufacturing process, API characteristics, excipients, and quality attributes of the drug product that may significantly impact the *in vivo* dissolution and bioavailability of the drug. A major recommendation to support the robustness of the established PBPK absorption model was challenging the model with *in vitro* and *in vivo* data of non-BE batches and/or batches with different releases.

Another topic Dr. Wu introduced was using PBPK absorption modeling to evaluate the impact of gastric pH change on drug pharmacokinetic (PK) and the potential impact on BE. For generic drugs, additional BE studies in subjects with altered gastric pH may be needed when there is gastric pH-mediated drug-drug interaction (DDI) that can be impacted by formulation where pH-modulating excipient(s) are present. A recently published product-specific guidance for palbociclib oral tablets recommends three *in vivo* BE studies including a fasting BE study in the presence of an acid-reducing agent (ARA) (2). One US FDA internal research project investigated whether PBPK absorption modeling can be used to evaluate the potential of such pH-dependent DDIs for four weak-base drugs including tapentadol, darunavir, erlotinib, and saxagliptin (3). The results suggested that PBPK absorption models developed could adequately describe the lack of the effect of ARAs on the PK of tapentadol, darunavir, and saxagliptin and could qualitatively predict the effect of ARA in reducing the absorption of erlotinib. For generic drugs, when there is formulation-dependent gastric pH-mediated DDI, additional BE studies in subjects with altered gastric pH may be useful, especially under certain high-risk situations. For example, a high risk exists when test products and comparator products contain different levels of pH stabilizing or modifying excipients. To demonstrate that a BE study in a gastric pH-altered situation may not be needed, scientific justifications, including pH-solubility profile, comparative dissolution testing at multiple pHs, and PBPK absorption modeling may be used. This can help avoid unnecessary human BE studies.

> Summary of Presentation "PBPK Modeling to Support Risk Assessment for Oral Drug Products, Including Waiver of Fed BE Studies" by Rebeka Jereb, PhD, Scientist, Lek Pharmaceuticals d.d., a Sandoz Company, Ljubljana, Slovenia[2]

[1] https://www.complexgenerics.org/media/SOP/complexgenerics/pdf/Conference-Slides/Modeling-Approaches/3-1%20Fang%20Wu.pdf

[2] https://www.complexgenerics.org/media/SOP/complexgenerics/pdf/Conference-Slides/Modeling-Approaches/3-2%20Rebeka%20Jereb.pdf

Dr. Jereb's talk focused on PBPK absorption modeling used during drug product development to support risk assessments. Generic companies adhere to health authority guidance on PBPK modeling to guide the modeling activities. The US FDA guideline on PBPK analyses for biopharmaceutics applications (4) is especially important as it focuses on drug product quality attributes and a mechanistic understanding of their interaction with physiology to affect the *in vivo* drug performance of oral products.

Dr. Jereb presented a case study of a risk assessment for an oral drug product with a BCS Class III drug, where BE was confirmed *in vivo*. A PBPK absorption model was used to assess the bio-relevancy of *in vitro* dissolution at low pH and the impact of non-similar dissolution profiles between test and reference on tablet performance *in vivo*. The model was developed gradually and properly validated using available *in vivo* data. Then, it was used to simulate *in vivo* dissolution using different stomach transit times, and the non-biorelevance of dissolution at low pH was confirmed. Dr. Jereb further discussed the current state of PBPK absorption modeling used for food effect predictions and options for waiving fed BE studies using PBPK absorption modeling.

There have been many publications in recent years reporting on the ability of PBPK absorption models to predict food effects (5–9). Riedmaier (10) suggested that after validation with *in vivo* data from studies in fasting conditions, models can be successfully applied to predict the fed state in lieu of a dedicated clinical food effect study. There remain some gaps, for instance, in the modeling of changes in transporter and enzyme kinetics in the presence of food. A middle-out approach can be applied with high confidence, where the fed model is validated with a clinical study and subsequently extrapolated to additional food effect questions, for example, following formulation or dosage changes. This approach could be applicable to generics, as food effect studies are usually conducted by the originator.

Dr. Jereb shared results from an analysis of six case studies (11) where the approach of predicting the results of the BE study in fed conditions using a PBPK absorption model developed on data from the BE study in fasting conditions and known food effect was evaluated. Some prerequisites identified as needed for successful prediction of BE in the fed state were BCS Class I or II drug with known food effect, preferably linear PK, reliable estimation of disposition parameters, available BE study data in the fasting conditions, and estimates of PK parameters variability.

Lastly, a case of waiving fed BE study submitted to the regulatory authority was presented. The model was developed and validated on numerous published and internal clinical data. The regulatory authority provided some suggestions for model improvement, e.g., that batches with different release rates *in vitro* and corresponding results *in vivo* should be used for model validation, preferably a batch with a non-bioequivalent result *in vivo*. The approach was not pursued further as the high standards for model validation could not be achieved.

> Summary of Presentation "Oral PBPK to Support BE Evaluation for Pediatric Drugs" by Hannah Batchelor, PhD, Professor of Pharmaceutics and Biopharmaceutics at Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde[3]

This presentation explored the use of biorelevant dissolution conditions to better reflect the characterization of the volume of GI fluids and the composition of these fluids in a pediatric population. The integration of the resulting profiles into the PBPK absorption model was used to identify the best match to existing PK data using carbamazepine tablets as a case example. BE of generic products is typically obtained using biowaivers based on adult systems or via the use of clinical testing in an adult population. BE obtained in adults is assumed to be extrapolatable when such products are used in a pediatric population. A PBPK absorption model for carbamazepine was developed using SimCyp® Simulator (Version 21, Certara UK Limited, Sheffield, UK) that incorporated drug-dependent and system-related input parameters obtained from SimCyp's internal compound library. The *in vitro* dissolution datasets were incorporated into the SimCyp® Simulator Advanced Dissolution, Absorption and Metabolism (ADAM) model. SimCyp Pediatric Version 21 was used as the pediatric PBPK (ped-PBPK) absorption modeling platform. Carbamazepine-specific properties (including its metabolic clearance) used in the adult PBPK model were transferred into the pediatric model. The performance of the model prediction was demonstrated using published clinical PK studies with carbamazepine (Tegretol© IR 100 or 200 mg) conducted in an adult population. The adult model was subsequently updated and applied to children (6–15 years) and further validated using clinical PK data conducted in children on 9 mg/kg dose ($n=6$) by Hartley *et al.* (12) and 20 mg/kg dose ($n=12$) by Bano (13). The most predictive dissolution data were identified as the suitable dissolution testing conditions (i.e., USP apparatus 2, 75 rpm, 500 mL adult Fasted State Simulated Gastric Fluid (FaSSGF) and Fasted State Simulated Intestinal Fluid (FaSSIF) dissolution medium). These dissolution data were then used for an innovator and generic product, and a VBE simulation was undertaken (two treatment, multiple trials ($N=10$) in a cross-over design with a sample size of $n=12$, 16, 24, 36, and 48 in healthy adults). The sample size of 12 was based on the real clinical study. Further, the

[3] https://www.complexgenerics.org/media/SOP/complexgenerics/pdf/Conference-Slides/Modeling-Approaches/3-3%20Hannah%20Batchelor.pdf

sample size was also increased from 12 to 16, 24, 36, and 48 to see whether the larger sample size will impact the predicted BE results. The most predictive dissolution data for integration into the pediatric PBPK absorption model was 200 mL pediatric media where the bile salt concentration or components used to represent the bile salts were less impactful on the predictive performance compared to the volume. The VBE study incorporating this dissolution showed equivalence between the formulations. The use of *in vitro* dissolution coupled with PBPK absorption testing is of immense value for pediatric products where testing in the end-user population is complicated by the ethical burden of conducting studies. Further work is ongoing to explore a wider range of drug products to better understand the wider use of a volume of 200 mL (as dissolution media) for pediatric populations; however, this work is limited due to the very low availability of good-quality clinical data in pediatric populations (particularly the very young) that can be used to validate the models developed. The identification of a biopredictive dissolution method for pediatric populations and subsequent integration of the generated dissolution data into PBPK absorption modeling can aid in de-risking pediatric clinical programs, specifically with reference to relative bioavailability studies or BE studies for generic drug products. As the purpose of this study is to assess BE between generic product and Reference Listed Drug (RLD) in pediatrics, this study mainly focused on the dissolution which can reflect the formulation differences between generic product and RLD and subsequently affect absorption of these two products. Regarding elimination uncertainty in pediatrics, as the elimination pathway of the generic product and RLD are the same in pediatrics, this research did not explore the differences in the elimination in pediatrics between these two products. The research results based on this work were just published (14).

Summary of Presentation "Approaches in Establishing BE Safe Space for Oral Solid Dosage Form" by Sumon Chakraborty, M. Pharm., Scientific Leader, Biowaivers, Biocorrelation and Statistical Support, Apotex, Canada[4]

Mr. Chakraborty discussed different approaches to establish BE safe space for oral solid dosage forms by presenting case studies for utilization of safe space to justify profile similarity and establish clinically relevant specifications.

In case study 1, the safe space concept was utilized to support lower strength biowaiver in case of similarity factor (F2) mismatch. The example drug product was an extended-release tablet for a BCS Class I compound with two strengths. The dissolution profile of the lowest strength was found to be faster compared to the highest strength in the quality control (QC) condition ($F2 < 50$). PBPK absorption modeling was conducted using GastroPlus™ to assess the impact of dissolution differences on *in vivo* performance under fasting condition. The dissolution data was integrated using the Weibull function. Plasma concentration was predicted for two batches (pilot and pivotal BE batch of highest strength) of the generic formulation with different release-controlling polymers and validated against the clinical study data. As a next step, the researcher conducted single simulations using a virtual batch with faster-release dissolution profiles (to represent the faster release from the lowest strength) and compared the predicted PK with that of a target pivotal BE batch with slower release dissolution profile (to represent the situation of the highest strength). The researcher found that the difference between predicted PK parameters (AUC and Cmax) between the virtual batch and pivotal BE batch was < 20%, indicating that the faster release of the virtual batch for the highest strength may not result in a non-BE to the target pivotal BE batch and justified that $f2 < 50$ between dissolution from the highest strength and lowest strength is not clinically relevant and the modeling and simulations can support biowaiver for lowest strength.

In case study 2, clinically relevant specifications were established based on PBPK model prediction. The example drug product is an IR capsule containing a BCS Class III drug substance. The original dissolution specification was $Q = 80\%$ at 30 min, as recommended by the regulatory authority. The objective of this PBPK modeling for biopharmaceutics analysis (it can also be termed a physiologically based biopharmaceutics model (PBBM)) was to widen the specification to $Q = 80\%$ at 45 min. The baseline model was developed using intravenous, oral solution, and IR capsule of different dose levels and validated against literature data. The model was further validated with the in-house clinical study data of the pivotal BE batch (generic and RLD product). The dissolution data of the bio-batches were entered directly into the PBPK model to simulate the plasma concentration profile. As the next step, several virtual dissolution profiles were created such that the virtual 1, virtual 2, virtual 3, and virtual 4 batches that release 80% of the drug at 30, 45, 60, and 75 min, respectively. Virtual 1 and 2 batches were anticipated to be bioequivalent against the generic BE batch (Target) based on the fact that the ratios of predicted PK parameters between the virtual batch and target batch were < 20%. It was demonstrated that the batch with the proposed specification of $Q = 80\%$ dissolved within 45 min met BE criteria. This analysis suggested that the extrapolation outside the knowledge space may be performed for highly soluble drug substance (BCS Class I/III) because the biopharmaceutics risk is usually low (15).

[4] https://www.complexgenerics.org/media/SOP/complexgenerics/pdf/Conference-Slides/Modeling-Approaches/3-4%20Sumon%20Chakraborty.pdf

Panel Discussion

To discuss and integrate the current thinking and knowledge gap regarding the use of mechanistic modeling approaches to support BE assessments for oral products, a panel discussion was conducted at the end of this session where representatives from regulatory agencies, industry, and academia were present. The panel discussion was moderated by Tycho Heimbach, PhD. (Biopharmaceutics Expert/Director, Biopharmaceutics & Specialty Dosage Group, Merck & Co., Inc, Rahway, NJ) and Ethan Stier, PhD (Associate Director, Lifecycle Management, Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS), CDER, FDA). Hannah Batchelor, PhD (Prof., Strathclyde Institute of Pharmacy and Biomedical Sciences, Univ. of Strathclyde); Sumon Chakraborty, M. Pharm. (Scientific Leader, Biowaivers, Biocorrelation and Statistical Support, Apotex); Rebeka Jereb, PhD (Scientist, Lek Pharmaceuticals d.d., a Sandoz Company, Ljubljana, Slovenia); Filippos Kesisoglou, PhD (Distinguished Scientist, Merck & Co., Inc., Rahway, NJ); Sivacharan Kollipara, MPharm (Team Lead, Biopharmaceutics, Dr. Reddy's Laboratories); Fang Wu, PhD (Senior Pharmacologist and Scientific Lead, DQMM, ORS, OGD, FDA); Yuching Yang, PhD (PBPK Co-Lead, Division of Pharmacometrics, Office of Clinical Pharmacology, Office of Translational Sciences, CDER, FDA); and Lei Zhang, PhD (Deputy Director, ORS, OGD, CDER, FDA) participated in the discussion panel. In the following part of this report, we have summarized the questions raised and discussed during this panel discussion.

Question 1

How Can PBPK Modeling Be Used as Part of the Risk Assessment for the Impact of Food on BE?

When using PBPK absorption modeling to do the risk assessment for the impact of food on BE, the following points should be considered: (i) mechanism of food effect including improved solubilization in the presence of bile salt, delay in gastric emptying time, altered stomach pH, involvement of transporters and complex interactions with food, (ii) understanding the role of formulation on food effect. For example, for low-solubility drug substances, the comparator product may be the result of an extensive formulation and/or manufacturing process development program, obtaining for instance a specific formulation without a food effect. If the test product uses a substantially different manufacturing technology or particle size control method from the comparator, or if substantially different types/levels of excipients are used in the test and comparator that are likely to impact solubility, dissolution, or permeability, this may suggest conducting BE studies under both fasting and fed conditions or using PBPK absorption modeling prediction to provide justifications of no significant food impact on BE to support a waiver of the fed BE study (iii) develop the model in fasting condition and validate it with in-house data (pilot data are useful), (iv) validate the model ability to predict the food effect for reference formulations by changing physiology and/or dissolution input (pilot data to validate the model) and using solubility and dissolution data generated in biorelevant conditions. To this last point, panelists commented that additional work across the biopharmaceutics community is needed to standardize which biorelevant media should be used for food effect predictions in PBPK absorption models, especially for the fed stomach. In addition, it is worth mentioning that normally, the physiology factors in the modeling platform are not changed as the platform has been previously verified unless specific situations were encountered. Under the specific situations, the modeling platform may need to be verified again.

Question 2

What Are the Consideration Points for Using PBPK Modeling to Evaluate the Impact of Gastric pH Change on Pharmacokinetics and BE?

For generic drugs, additional BE studies (e.g., in subjects with altered gastric pH) may be useful when there is formulation-dependent gastric pH-mediated DDI (2). The risk is high under certain situations, e.g., when test products and comparator products contain different levels of pH stabilizing/modifying excipients. Dissolution profiles, which significantly vary from acidic to neutral pH, can indicate a pH-dependent dissolution. Using PBPK absorption models to predict ARAs or proton pump inhibitor (PPI)-based DDI is an important step towards identifying formulation-dependent DDI. Important input data for the PBPK absorption model include the pH-solubility profile or biopredictive dissolution testing at multiple pHs. Integration of these aspects into the model and further changing gastric pH as part of a parameter sensitivity analysis can provide an assessment for the impact of gastric pH change on systemic exposure as the physiological gastric pH can be altered depending on the co-administered ARAs.

Note that generally, gastric pH-mediated DDI studies are conducted with or include a PPI as a worst-case scenario. So, the panel discussion covered the effect of PPI on gastric pH and did not cover other DDI mechanisms for some ARAs such as reduced absorption due to the formation of chelate complexes (e.g., aluminum or magnesium hydroxides, calcium carbonate) for weak-acid drugs or decreased renal

elimination of certain drugs as a result of the alkalinization of urine (e.g., sodium bicarbonate).

Question 3

When Generic Companies Are Developing PBPK Models for Regulatory Purposes for Different Scopes, for Example US FDA, EMA, or Japan, Are There Any Differences in Model Development and Validation?

The guidelines issued by the US FDA and the European Medical Agency (EMA) are similar. In these guidelines, there are no criteria for model validations. All of these guidelines request proper justifications of model and drug substance/product attributes and inclusion of *in vivo* data from PK and/or BE studies for validation. Additionally, the mechanistic framework (i.e., ADME) of the model needs to be justified appropriately in order to describe its ability to capture all *in vivo* processes.

Question 4

What Challenges Are Generics Companies Facing When Developing and Validating PBPK Models for Risk Assessments for Oral Drug Products?

The following challenges were mentioned in the panel discussion: (i) The modeler needs to demonstrate the bio-discriminating capability of the PBPK absorption model. While there are not enough data for model development/validation, especially challenges with the availability of non-BE batch and the need of validating the model by rejecting the non-BE batch. (ii) Difficulties with identifying bio-predictive *in vitro* methods, e.g., QC media not being bio-predictive. (iii) Default software values (pH, fluid volume) may not be biorelevant. For example, the default gastric pH does not reflect the pH changes after co-administration of PPIs. When PBPK modeling and pH-dependent solubility profiles are used to predict the impact of gastric pH on bioavailability, the default gastric pH is around 1.2, which may need to be changed to around pH 6 to reflect the biorelevant situation. (iv) Under some situations, dissolution may not be considered a critical bioavailability attribute. Difficulties in *in vivo* predictions where exposures are not governed by dissolution alone especially for IR formulations. (v) Unavailability of model input parameters/optimization (e.g., enzymes/transporters) for PBPK absorption models. (vi) Inability to reach low prediction errors (e.g., below 10%) when combining data from different studies, for different doses and formulations, especially for highly variable drugs, (vii) no specific guidance available on the procedure of determining virtual dissolution profile to find out the edge of failure study.

Question 5

What Are the Different Methods Available to Integrate *In Vitro* Data into PBPK for Its Intended Application? What Criteria Should Be Used to Select an Appropriate Method? How Reliable Are the PBPK Tools Without the Integration of the Dissolution Aspect?

The use of dissolution data as model input is applicable if dissolution is a governing factor for *in vivo* exposures (i.e., modified release (MR) formulations or dissolution rate limited IR formulations). However, in certain cases, precipitation may be present, especially for weak base drugs. When dissolution is a key factor (critical bioavailability attribute), different input methods need to be used for IR and MR formulations. There are successful examples in the literature demonstrating IR products may use the direct dissolution data input, *Z*-factor, Weibull functions or product particle size distribution (P-PSD) approaches (16, 17). For example, a direct input approach can be used for products which have condition-independent dissolution profile (e.g., BCS Class I/III IR drug products or osmotic pump products). *Z*-factor or P-PSD approach can be used for BCS Class II/IV drug products, where the lag phase or plateau phase cannot be fitted with *z*-factor but is possible using P-PSD. Additionally, while fitting dissolution data with the *z*-factor (Takano) model (18), special considerations have to be made with regard to disintegration time, goodness of the fit, and coning in the dissolution vessel. MR products may use direct input, *in vitro in vivo* relationship (IVIVR)/time scaling, or Weibull fitting approaches for the development of IVIVC.

Panelists discussed the importance of understanding the mechanism of dissolution and the selection of an appropriate dissolution model. Data from QC and biorelevant dissolution media could be used if the dissolution method is biorelevant/bio-predictive. Semi-mechanistic models should be generally preferred over direct dissolution input as described in the preceding paragraph—but direct dissolution input could be an option if qualified with a non-BE batch. Panelists deemed the *z*-factor model to be useful for IR products if they have a complete release. However, the *z*-factor model may not be appropriate if the release is incomplete because it depends on the initial release phase and cannot capture the whole dissolution process. P-PSD can be used as an alternative (17). The importance of the bio-discriminating capability of the PBPK absorption model with dissolution inputs against available clinical data (preferably batches exhibiting failed BE) was discussed.

Question 6

Is It Feasible to Expand the Safe Space Beyond the Knowledge Space? What Are the Criteria to Satisfy the Case?

From an industry perspective, using a non-BE batch to define knowledge space (KS) may not be practical. Especially for generic companies, manufacturing a non-BE batch is not usually performed, and hence, the possibility of extrapolation of data beyond the KS needs to be explored. Extrapolation beyond the KS may be possible if the target product is a low biopharmaceutics risk product (15), e.g., IR product with highly soluble drug substance, or IR product with BCS Class II drug substance with rapid dissolution in basic pH without surfactant, or IR product with BCS Class II drug substance with complete and rapid dissolution at gastric pH and without significant precipitation at intestinal pH. However, sensitivity analysis by a validated PBPK absorption model can help identify which parameter is a critical factor for impacting PK and support further evaluation for setting a safe space. One also needs to take into consideration the level of risk of non-BE and the totality of the data. Panelists recommended that this is an opportunity for the biopharmaceutics community to better define scenarios where there is a high confidence in extrapolation and the associated best practices. This would enable wider use and impact of PBPK absorption modeling and constrain it to interpolation between existing clinical datasets.

Conclusions

The use of PBPK absorption modeling and simulation approaches in the regulatory submissions for the drug development is continuously evolving. This workshop session discussed recent topics including using PBPK absorption modeling for evaluating the impact of food and gastric pH on BE and extrapolation of BE from adults to pediatrics. During the workshop, successful cases and views on the best practices, challenges, and opportunities on the utility of PBPK absorption modeling in these areas were shared. The key takeaways from this session of the workshop are that with more successful cases on PBPK absorption modeling being developed and shared, the general strategies/frameworks on using PBPK absorption modeling for oral products are being formed, and the consensus is reached; this will help further evolvement of this area. In addition, the early communications between the industry and the agency through appropriate pathways (e.g., pre-ANDA meetings) are encouraged, and this will speed up the successful development and utility of PBPK absorption modeling for oral products.

Author Contribution FW, YM, RJ, HB, and SC contributed to the writing of the manuscript. TH, ES, FK, SK, LZ, and LZ provided critical feedback and helped in shaping the manuscript. All authors contributed to drafting/revising of the content and final approval of the version to be published.

Funding This workshop was supported by the Food and Drug Administration (FDA) of the US Department of Health and Human Services (HHS) as part of a financial assistance award U18FD007054 totaling $1,000,000 with 100% funded by FDA/HHS.

Declarations

Conflict of Interest The authors declare no competing interests.

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