The AAPS Journal (2021) 23: 31
DOI: 10.1208/s12248-021-00564-2

Commentary

Biopharmaceutics Applications of Physiologically Based Pharmacokinetic Absorption Modeling and Simulation in Regulatory Submissions to the U.S. Food and Drug Administration for New Drugs

Fang Wu,[1,2,9] Heta Shah,[3] Min Li,[1] Peng Duan,[3] Ping Zhao,[4,5] Sandra Suarez,[3] Kimberly Raines,[1] Yang Zhao,[1,6] Meng Wang,[1,7] Ho-pi Lin,[1] John Duan,[3] Lawrence Yu,[8] and Paul Seo[1,9]

Received 16 October 2020; accepted 1 February 2021; published online 22 February 2021

Abstract. Physiologically based pharmacokinetic (PBPK) absorption modeling and simulation is increasingly used as a tool in drug product development, not only in support of clinical pharmacology applications (e.g., drug-drug interaction, dose selection) but also from quality perspective, enhancing drug product understanding. This report provides a summary of the status and the application of PBPK absorption modeling and simulation in new drug application (NDA) submissions to the U.S. Food and Drug Administration to support drug product quality (e.g., clinically relevant dissolution specifications, active pharmaceutical ingredient (API) particle size distribution specifications). During the 10 years from 2008 to 2018, a total of 24 NDA submissions included the use of PBPK absorption modeling and simulations for biopharmaceutics-related assessment. In these submissions, PBPK absorption modeling and simulation served as an impactful tool in establishing the relationship of critical quality attributes (CQAs) including formulation variables, specifically *in vitro* dissolution, to the *in vivo* performance. This article also summarizes common practices in PBPK approaches and proposes future directions for the use of PBPK absorption modeling and simulation in drug product quality assessment.

KEY WORDS: biopharmaceutics; clinically relevant drug product specifications (CRDPS); dissolution; physiologically based pharmacokinetics (PBPK); quality risk assessment.

[1] Division of Biopharmaceutics, Office of New Drug Products, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, Maryland 20993, USA.
[2] *Present Address:* Division of Quantitative Methods and Modeling, Office of Research and Standard, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, Maryland 20993, USA.
[3] Division of Biopharmaceutics, Office of New Drug Products, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, 20993, USA.
[4] Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, 20993, USA.
[5] *Present Address:* Bill & Melinda Gates Foundation, Seattle, Washington 98109, USA.
[6] *Present Address:* Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, 20993, USA.
[7] *Present Address:* Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, 20993, USA.
[8] Office of New Drug Products, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland 20993, USA.
[9] To whom correspondence should be addressed. (e–mail: Fang.Wu@fda.hhs.gov; Paul.Seo@fda.hhs.gov)

INTRODUCTION

Physiologically based pharmacokinetic (PBPK) absorption modeling and simulation (M&S) (also referred to as physiologically based biopharmaceutics modeling when PBPK analyses are for biopharmaceutics applications) integrates gastrointestinal (GI) tract anatomical and physiological aspects with drug physicochemical and absorption, distribution, metabolism and excretion (ADME) properties to predict *in vivo* drug exposure (1). The model uses the understanding and prediction of the drug disposition in the GI tract through dissolution, precipitation, metabolism and absorption process. When combining this information with a pharmacokinetics (PK) model, PBPK M&S allows for the prediction of plasma drug concentration-time profiles (1, 2). The application of physiologically based absorption modeling in drug development was introduced over two decades ago (1). Initially the exploration of this approach primarily focused on drug absorption and pharmacokinetic (PK) prediction in support of formulation development (3). This approach has gained interest more recently and is increasingly utilized in areas such as drug discovery, formulation development, quality risk assessment and *in vivo* bioequivalence (BE) simulation (4–9). PBPK absorption M&S has

become a valuable tool in biopharmaceutics assessment when determining the impact of the physicochemical properties of the drug, the critical quality attributes of the drug product, and the route of administration on the rate and extent of systemic drug absorption.

Regulatory agencies have recognized the utility of PBPK and have brought forth guidance to industry to provide standards and best practices. The U.S. FDA issued the "Physiologically Based Pharmacokinetic Analyses – Format and Content" final guidance in 2018 to provide recommendations for sponsors and applicants on the format and content of PBPK analyses submitted to the FDA to support applications including investigational new drug applications (INDs), new drug applications (NDAs), biologics license applications (BLAs), and abbreviated new drug applications (ANDAs)(10). Recently in October 2020, U.S. FDA issued the "The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls" draft guidance to provide general recommendations regarding the development, evaluation, and use of PBPK analyses for biopharmaceutics applications (11). The European Medicines Agency (EMA) also published "Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation" in 2018 (12), which details what to include in a PBPK modeling report to allow assessment of the predictive performance of the drug model.

In NDAs, PBPK absorption M&S has been used for drug-drug interaction (DDI) prediction, evaluation of food effect, dose selection in specific populations (e.g., patients with hepatic or renal impairment, pediatric patients, pregnant women, individuals with generic polymorphism) in the area of clinical pharmacology (13–17). In generic drug development, PBPK absorption M&S has been used for product-specific guidance development, comparative clinical endpoint bioequivalence (BE) study design and supporting ANDA assessments (4). The U.S. FDA is advocating patient-centric quality assessment with the ultimate goal of assuring consistent efficacy and safety over the lifecycle of drug products (18). In this regard, the PBPK absorption M&S approach can facilitate the control of product quality towards clinical outcomes using parameter sensitivity analysis (PSA) and virtual bioequivalence simulation, leading to the establishment of clinically relevant drug product specifications (CRDPS)(19). For these reasons, PBPK absorption M&S can be an important tool for biopharmaceutics-related assessment. This review outlines the status of PBPK absorption M&S approach and its application for drug product quality assessment in NDA submissions, and summarizes some of the common practices and future directions of the PBPK absorption M&S in establishing clinical relevance in drug product quality.

STATUS OF PBPK ABSORPTION M&S APPROACH FOR BIOPHARMACEUTICS ASSESSMENT IN NDA SUBMISSIONS

NDA submissions received by U.S. FDA between January 2008 to December 2018 were surveyed, and a total of 24 cases were found containing PBPK absorption M&S for biopharmaceutics application (Fig. 1). These cases encompass both immediate release (IR) (18 out of 24, i.e., 75%) and extended-release(ER) (6 out of 24, i.e., 25%) solid oral dosage formulations involving all categories of Biopharmaceutical Classification System (BCS) classification drugs (71% of these drugs are BCS II or IV drugs). There is a trend to increasing use of PBPK absorption M&S in NDA submissions from 2008 to 2015, which may be due to an increase in awareness and better understanding of the applicability of PBPK modeling in the pharmaceutical industry along with increasing commercial software capabilities. The number of submissions at NDA stage decreased from 2015 to 2018, which may be due in part to applicants submitting pre-NDA filing (e.g., IND stage) to increase the opportunity to have early communications with U.S. FDA. Figure 2 and Table I depict the applications of PBPK absorption models within the identified NDA submissions. The applications can be categorized as (1) setting clinically relevant dissolution specifications that can ideally reject batches with undesired in vivo performance, which involves both the selection of bio-predictive dissolution methods (i.e., a set of testing conditions for which in vitro dissolution profiles are capable of predicting PK profiles), and the establishment of clinically relevant dissolution acceptance criteria; (2) setting clinically relevant specifications for critical material attributes (CMAs) and critical process parameters (CPPs) (e.g., in support of particle size distribution specification based on the effect of particle size on *in vivo* absorption); and (3) supporting quality risk assessment and possible risk-based biowaiver request (e.g., via physiologically based *in vitro* and *in vivo*correlation/relationship (PB-IVIVC/R) or virtual BE trial simulation). Other applications are sporadically seen, such as drug absorption prediction in pediatrics for formulation selection, the evaluation of the effect of gastric pH or food on drug absorption, and predicting bioavailability.

COMMON APPLICATIONS OF PBPK ABSORPTION M&S IN NDA SUBMISSIONS FROM A DRUG PRODUCT QUALITY PERSPECTIVE

Establishing Clinically Relevant Dissolution Specifications

One common application of PBPK absorption M&S from the perspective of drug product quality is to support the establishment of clinically relevant dissolution specifications, resulting in many cases in wider acceptance criteria and therefore regulatory flexibility. In one submission case, a validated PBPK model was employed to support the proposed dissolution acceptance criteria for a proposed immediate release solid oral drug product containing multiple strengths. The Q value of 75% at 30 min was supported by PBPK simulation for the highest strength as the virtual batch (representing a virtual dissolution profile with Q=75% at 30 min, which was directly incorporated into the PBPK model) and the reference pivotal BE batch was predicted to be bioequivalent based on virtual BE results. The same criterion was not supported by the virtual BE simulation for two lower strengths as the virtual release profiles did not predict bioequivalence to the respective reference batches. However, virtual BE simulation results

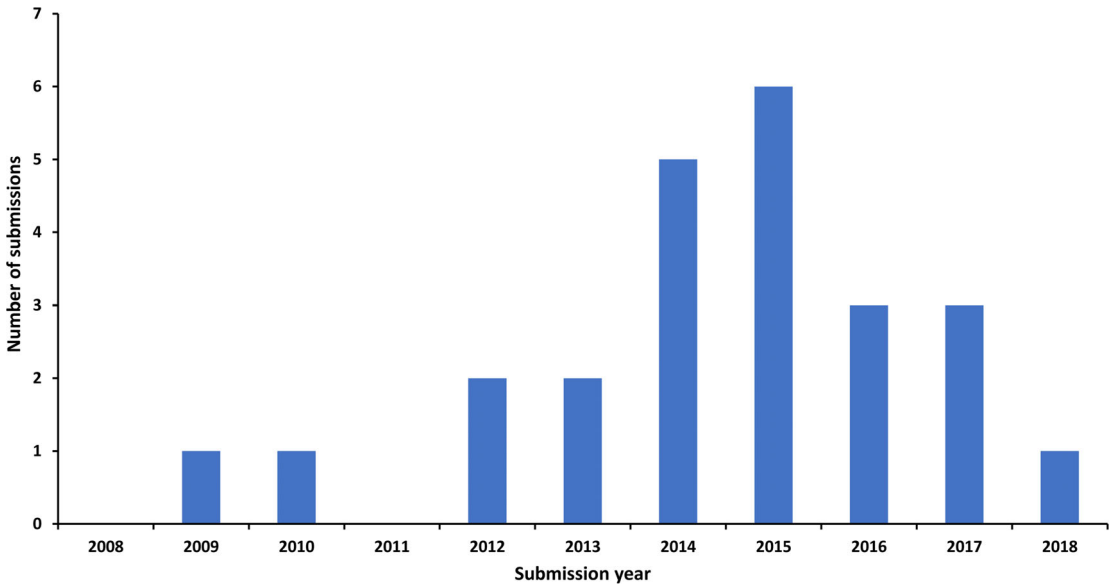

Fig. 1. Number of new drug applications containing PBPK absorption modeling and simulations for biopharmaceutics assessment from January 2008 to December 2018 (Investigational New Drugs are not included)

along with the observed in vitro dissolution data supported a dissolution acceptance criterion of Q = 80% at 30 min for the two lower strengths. Data demonstrate that the PBPK model can accurately predict the systemic exposure of non-BE batches via virtual BE analysis, rendering the dissolution specifications bio-predictive. The use of PBPK absorption M&S provided regulatory flexibility that a wider in vitro dissolution acceptance criterion could be supported for the higher strength. Table II provides a total of four submission cases where PBPK absorption models were used to justify the discriminating and bio-predictive capability of the *in vitro* dissolution method, and aid in setting clinically relevant dissolution acceptance criteria.

Presented in Table II is a submission case of applying PSA using an established PBPK model to aid in the setting of a "safe space" (e.g., upper and lower limits are BE to target batch) for *in vitro* dissolution profile (i.e., release rate) and to justify a wider dissolution acceptance criterion (e.g., Table II—Drug D). PSA is a mathematical tool that allows determination of how the change in one parameter affects model prediction. PSA can identify parameters that contribute to the variability of the PK profile, which can be used to inform model optimization. For Drug D, PSA was performed, and the result showed that the modest changes in the dissolution rate (modelled using the z-factor) had no impact on the drug amount entering the portal vein;

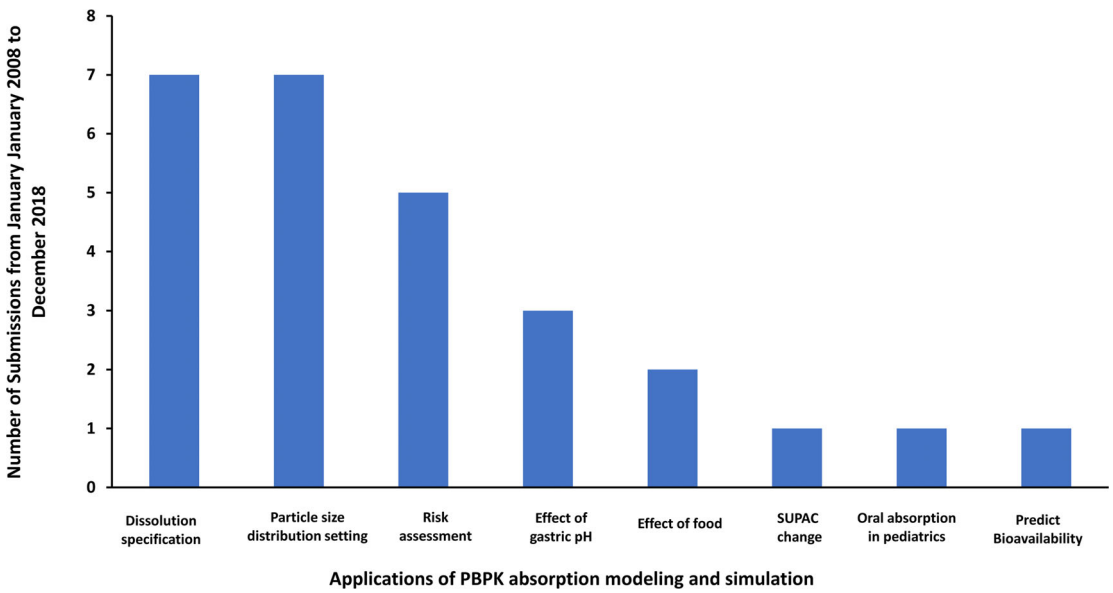

Fig. 2. Applications of PBPK absorption modeling and simulations in the new drug applications submissions*. Abbreviations: SUPAC, scale-up and post-approval changes. *Note that in some cases, the same model was used for multiple purposes, e.g., setting of both particle size specification and dissolution acceptance criteria

Table I. The Applications and Current Approaches of Physiologically Based Pharmacokinetic Modeling and Simulation in Biopharmaceutics Assessment

	Main application	Current approach
Dissolution method and acceptance criteria	To justify discriminatory capability of dissolution method	Use a validated PBPK absorption model combined with bioequivalence clinical study and dissolution profiles to show that the proposed dissolution method can reject non-BE batch
	To set patient-centric dissolution acceptance criteria	Used to allow wider dissolution acceptance criteria
Set patient-centric controls of CMAs and CPPs	To define CMAs (e.g., particle size, polymorphic form)	Used to predict the effect of upper limit of API particle size distribution on the *in vivo* performance of drug product Used to predict the effect of API polymorphic form on *in vivo* performance of drug product
	To establish CPPs (e.g., milling method, compression force)	Used to evaluate the impact of the proposed change of milling method on *in vivo* performance of drug product as milling method is linked to particle size Used to justify specification range of compression force based on the predicted *in vivo* performance of drug product
Quality risk assessment	To assess risk related to pre-approval changes or SUPAC changes	Used in combination with dissolution similarity test to perform risk assessment on Chemistry Manufacturing Control changes based on parameter sensitivity analysis and virtual BE prediction Mechanistic IVIVC based on PBPK absorption model to increase the success rate of IVIVC prediction for supporting biowaivers

Notes: *PBPK*, physiologically based pharmacokinetic model; *M&S*, modeling and simulations; *CMA*, critical material attributes; *CPP*, critical process parameters; *IVIVC/IVIVR*, in vitro in vivo correlation/relationship; *SUPAC*, scale-up and post-approval changes; *API*, active pharmaceutical ingredient

therefore, impact on PK is expected to be minimal. In general, when a safe space for dissolution is defined, any movement within the pre-defined range could be justified to be in line with consistent *in vivo* drug product performance (i.e., bioequivalent to reference products). These submission cases demonstrate that PBPK absorption M&S is a promising tool for supporting clinically relevant dissolution specifications, to ensure the capability to reject batches with unsatisfactory *in vivo* performance.

It is worth noting that PBPK absorption modeling has been used to aid in *in vitro in vivo*correlation/relationship (IVIVC/R) model development and support setting dissolution acceptance criteria (e.g., Drug C). IVIVC represents a relationship between the *in vitro* quality attributes of a dosage form (e.g., drug product release profiles) and its *in vivo* performance (e.g., concentration-time profiles) (20). In vitro-in vivo correlation (IVIVC) is a predictive mathematical model describing the relationship between in vitro drug release rates and in vivo drug absorption profiles. While an in vitro-in vivo relationship (IVIVR) is a rank-order relationship established between in vitro release profiles and a relevant in vivo response. Comparing to the conventional mathematical IVIVC model development, a PBPK approach shows promising advantages for designing IVIVC in a mechanistic framework. For a physiologically based/mechanistic IVIVC, *in vivo* absorption is deconvoluted through a mechanistic absorption model which separates gut/intestine transit, permeation, gut wall metabolism, and first pass metabolism input from *in vivo* dissolution (21)(Fig. 3). Thus, the physiologically based IVIVC not only allows one to establish the correlation of *in vitro* dissolution and *in vivo* absorption, but also facilitates the incorporation of factors such as formulation (22), metabolism/transport, population variance (23), and food effect (24), and takes nonlinear pharmacokinetics into consideration. The advantages of a PBPK-based approach may translate into increased success rate of IVIVC/R models in general, particularly with the considerations of drug *in vivo* dissolution and absorption mechanisms under physiological conditions (25). As such, PBPK absorption modeling principles have been incorporated in the development of *in vitro in vivo*correlation/relationship (IVIVC/R). For example, in a recent NDA submission, physiologically based IVIVR was explored to support the setting of clinically relevant dissolution specifications. In the case for Drug C (Table II), the developed physiologically based IVIVR was used to predict a rank-order relationship between the pharmacokinetic behavior from the *in vitro* dissolution profiles and was able to demonstrate the discriminating and bio-predictive ability of the proposed *in vitro* dissolution method.

Clinically Relevant Drug Product Specifications

Establishing clinically relevant drug product specifications through the linkages between the identified CMAs, CPPs, critical quality attributes (CQAs) (e.g., dissolution), and *in vivo* performance are key elements for patient-centric assessment of quality (25). CRDPS are those that take into consideration the clinical impact of variations in the CMAs and CPPs. They are established with the intent of ensuring adequate safety and efficacy throughout the drug product's lifecycle. Increased understanding of the impact of those CMAs and CPPs on in vivo performance can lead to setting of more relevant controls, consistent with a patient-centric approach to quality. It is important to set clinically

Table II. Examples of Physiologically Based Pharmacokinetic Absorption Modeling and Simulations for Justifying the Discriminating and Bio-predictive Capability of the *In Vitro* Dissolution Method and Setting Patient-Centric Dissolution Acceptance Criteria

	Drug A	Drug B	Drug C	Drug D
Dosage form	Immediate release tablets	Immediate release tablets	Extended release tablets	Immediate release capsules
BCS claim	BCS class IV	BCS class II	BCS class I	BCS class IV
Method for incorporating dissolution in the model	Weibull dissolution model Dissolution data is used for Weibull model fitting	Johnson dissolution model The product-particle size distribution estimated from the in vitro dissolution profile was used as model input	Dissolution profile data are directly incorporated	z-factor dissolution model based on the in vitro dissolution data obtained from biorelevant dissolution testing
Model development methods (e.g., optimized parameters)	The parameters (P_{eff}, Pgp Vmax, CYP3A4 Vmax, $CL_{h,\ int}$ and Kp) were optimized.	Gastric emptying pattern and P_{eff} were fitted based on the observed pharmacokinetic profiles of individual subjects. Volume occupation by water in the small intestine and colon are optimized.	P_{eff} was optimized using *in vivo* data from oral administration. Absorption scale factor were also optimized.	A fixed hepatic first pass value was derived from the clinical study data. The Km of CYP3A4 and Pgp was the experimental value and Vmax was optimized Mean Precipitation Time was optimized to a high value to keep supersaturation.
Model validation	The model prediction can discriminate a non-BE batch.	The model prediction can discriminate a non-BE batch.	An IVIVR model predicted mean data from the clinical study with subjects dosed at a higher dose.	The model was validated by matching the pharmacokinetic profiles of two different single oral doses and one intravenous dose.
Results	The *in vivo* prediction from the model indicated the test batches are BE to the reference drug product.	The model prediction justified that the proposed dissolution specification was able to reject batches that are non-BE to the reference drug product.	The physiologically based IVIVR model predicted bioequivalence between test and reference formulation.	Using parameter sensitivity analysis, the result showed changes in the dissolution rate (z-factor) had no impact on the amount entering the portal vein.
Regulatory decision	The PBPK absorption M&S supports the proposed dissolution specification as bio-predictive	The PBPK absorption M&S supports the proposed dissolution specification as patient-centric.	The PBPK absorption M&S supports the proposed dissolution specification as bio-predictive	A risk-based approach, the proposed acceptance criterion is acceptable.

Notes: *BCS*, Biopharmaceutics Classification System; P_{eff}, effective permeability; *Pgp*, P-glycoprotein; *Vmax*, maximum transport rate or maximum rate of metabolite formation; *CYP*, cytochrome p450 enzyme; *CL*, clearance; $CL_{h,\ int}$, hepatic intrinsic clearance; *Kp*, tissue-to-plasma partition coefficient; *PBPK*, physiologically based pharmacokinetic model; *M&S*, modeling and simulations; *BE*, bioequivalence; *IVIVR*, in vitro in vivo relationship; *Km*, Michaelis-Menten constant; *Cmax*, maximum drug concentration; *AUC*, area under the curve

relevant CMA and CPP controls for driving patient-centric drug product quality. CMAs include, but are not limited to, API particle size, polymorphic form, and excipient amount. CPPs include, but are not limited to, milling, blending, granulation, and coating parameters, and compression parameters such as force and duration. Ideally, BA and BE measurements should be employed to investigate the impact of changes in the CMAs and CPPs on clinical outcomes. However, conducting BA/BE studies for every formulation/manufacturing change in relation to clinical batch formulation is impractical and poses a huge burden to the pharmaceutical industry. In this regard, the PBPK absorption M&S is a promising tool and when properly validated, it has the potential to lower this burden as it offers a platform where prior knowledge on dissolution related to drug product manufacturing and formulation variants and its resulting systemic exposure may be leveraged in supporting the predictions of in vivo performance with expanded/widened range of CMAs and CPPs. It is worth noting that current commercial software has limitations incorporating CMAs and CPPs in PBPK absorption modeling as only API particle size distribution (PSD) and *in vitro*dissolution/release data are considered model inputs for *in vivo* prediction. Furthermore, when using *in vitro*dissolution/release data as a model input, the accuracy of the predictions will highly depend on the discriminating and bio-predictive abilities of the *in vitro*dissolution/release method used for generating the input data and the adequacy of the dissolution model selected for fitting. The dissolution models that are incorporated into the PBPK model generally include Johnson, Wang-Flanagan and z-factor models. Examples are described below. The Johnson dissolution model, which accounts for the particle size changes, may be the most appropriate for cylindrical particles (26). The Wang-Flanagan dissolution model is appropriate only to spherical particles (27), whereas the z-factor model does not take into consideration the diffusion coefficient adjustment due to bile salts (28). Also, for weak base drugs that can dissolve in the stomach and might potentially precipitate in the small intestine, certain parameters such as particle shape factor may also play a role in absorption phenomena and model

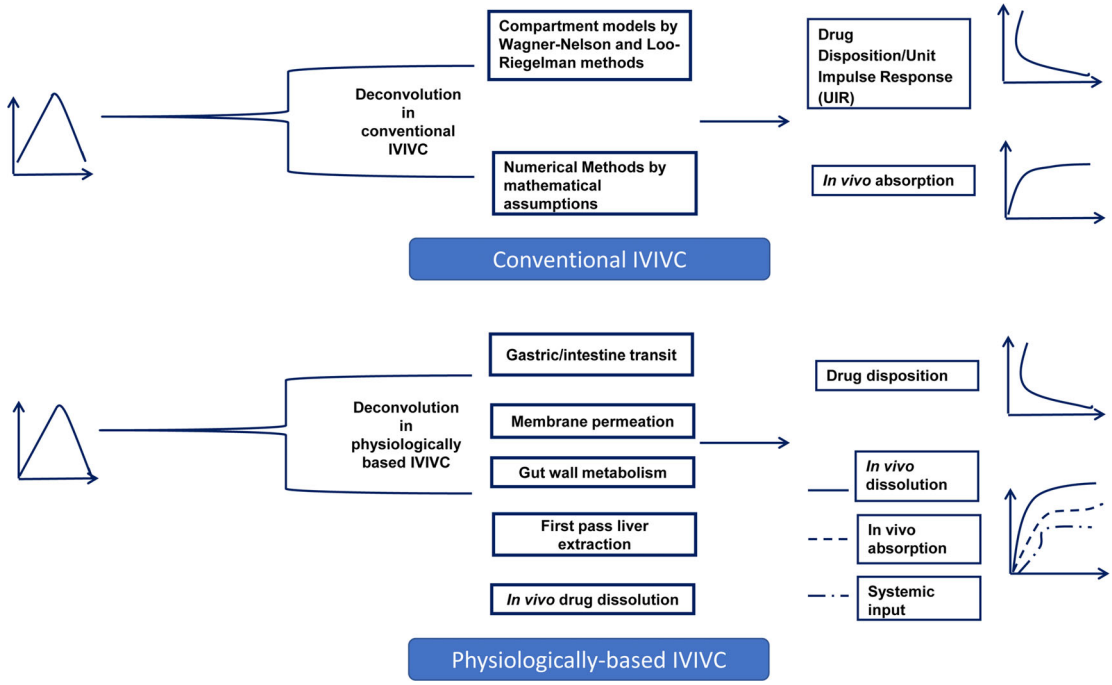

Fig. 3. Differences in deconvolution between conventional IVIVC and physiologically based IVIVC. Abbreviations: IVIVC, in vitro in vivo correlation

predictive capabilities. By considering the above parameters and respective release mechanisms, an appropriate mechanistic PBPK model could be established and used for setting controls of particle size of APIs, especially for BCS class II (low solubility, high permeability) and IV (low solubility, low permeability) drugs for which API particle size may be an important factor in clinical performance due to effects on dissolution.

The submission cases summarized in Table III demonstrate that PBPK absorption M&S can support setting controls for CMAs to ensure product with satisfactory *in vivo* performance (e.g., bioequivalent to target/reference batch). One of these cases (Drug F) also relied on parameter sensitivity analysis to assess the sensitivity of API particle size on drug exposure and to identify the range/upper limit of particle size that will have significant impact on *in vivo* performance. Specifically, the results of these simulations on absorption indicated that there would be insignificant changes, if any, in the fraction of drug absorbed when considering the proposed upper limit on API particle size. In addition, virtual BE trials combined with risk-based assessment have been used to compare the predicted BE across specific ranges of particle size and to help define the specification of the particle size (Drug E and Drug G). In addition, PBPK absorption M&S could take into account population variabilities when needed (e.g., via population simulator). Drug E showed that taking into consideration the intra- and inter-subject variability of the critical model parameters (e.g., permeability, gastric emptying time) in certain cases can improve model prediction. The advantage of the population simulator is that, unlike two-dimensional PSA where only one parameter is tested at a time while holding all other parameters constant, the values of all selected physiological and pharmacokinetic parameters are randomly defined and sampled.

Application of PBPK M&S in Risk Assessment

PBPK M&S has also been used in support of risk assessment in NDA submissions. For example, PBPK model predictions were used to support that the inclusion of isolated monohydrate drug substance form in the final drug product would not affect its absorption. In this case, the pharmacokinetic disposition parameters were derived from the observed concentration-time profiles after intravenous (IV) administration of Drug H (BCS class IV drug, modeling details are not provided in the table). To establish the absorption model for Drug H polymorphic form, the biopharmaceutics parameters specific for the original polymorphic form were adjusted with those for polymorphic form 2 of Drug H. The model was validated at three different dose levels with available clinical data in healthy volunteers under both fasted and fed conditions. A sensitivity analysis on z-factor was performed to explore the dependency of the PK parameters (AUC and Cmax) on the dissolution rate. The simulation outcomes were subsequently compared to the *in silico* results for the polymorphic form 1. Based on the virtual BE results, it was concluded that the slower dissolution rate due to polymorphism would not have significant effect on drug exposure.

Generally, sensitivity analysis and virtual BE simulations have been used to aid in risk assessment. For example, parameter sensitivity analysis was performed to identify the range of z-factor that would have no significant impact on *in vivo* performance (Drug H). The virtual BE simulations help justify the range of z-factor within which the batches with those release rate characteristics were bioequivalent to the bio-batches. These virtual BE simulations for batches with different z-factor characteristics combined with risk-based assessment help define the design space for CQAs to mitigate the risk of non-BE.

Table III. Examples of Physiologically Based Pharmacokinetic Absorption Modeling Approaches for Setting Particle Size Distribution Limits for Active Pharmaceutical Ingredients

	Drug E	Drug F	Drug G
Dosage forms and BCS class	Immediate release tablets BCS class IV	Immediate release tablets BCS class II	Immediate release tablets BCS class IV
Method for incorporating dissolution in the model	Johnson model Particle size and solubility were integrated in PBPK model and use Johnson dissolution model for dissolution simulation	Johnson model Particle size and solubility were integrated in PBPK model and use Johnson dissolution model for dissolution simulation	Johnson model Particle size and solubility were integrated in PBPK model and use Johnson dissolution model for dissolution simulation
Model establishment	Rate constants and total clearance were estimated. Gastric emptying time and P_{eff} were individually fitted and disposition parameters were kept constant.	CL_{int} was estimated from the observed data. P_{eff} was estimated by the ADME predictor.	Particle size distribution data of multiple batches was incorporated. First-pass extraction in liver and gut were estimated Multiple sets of clinical data were used for model training.
Model validation	Validated by the *in vivo* data from one test batch failed in the BE study and one batch passed the BE study. The model prediction can discriminate the non-BE batch.	Simulated plasma concentrations were able to capture observed pharmacokinetic data	Validated by multiple sets of clinical data.
Results	Batches that meet the proposed specification limit are bioequivalent to the clinically tested material with no appreciable difference in C_{max}, T_{max} and AUC.	Parameter sensitivity analysis indicates that the influence of particle size on the absorption is negligible when the mean particle radius is under a certain limit. The 90% CI results showed that the formulation with the particle size of the worst-case scenario (upper bound of the PSD) is BE to the clinical formulation.	Virtual BE was conducted using a reference batch with the proposed lower bound of PSD (based on clinical batch) and a test virtual batch with the proposed upper bound of PSD. Based on the simulation, the upper bound of PSD was defined by reaching BE to the proposed lower bound of PSD.
Regulatory decisions	The proposed PSD limits were justified.	The proposed PSD limits were justified.	Based on the virtual BE results, PSD D_{90} was defined.

Notes: *BCS*, Biopharmaceutics Classification System; *PSD*, particle size distribution; P_{eff}, effective permeability; C_{max}, maximum drug concentration; T_{max}, time to reach maximum drug concentration; *AUC*, area under the curve; CL_{int}, intrinsic clearance; *ADME*, absorption, distribution, metabolism, and excretion; *CI*, confidence interval; *D90*, the diameter where ninety percent of the particles has a smaller particle size

Other Applications of PBPK Absorption M&S in Addressing Absorption Related Issues

PBPK absorption M&S has also shown its potential in evaluating food effect (29) and predicting the effect of gastric pH on drug absorption/bioavailability for drugs with pH-dependent solubility (30). In one NDA submission, a PBPK absorption model was used to simulate the effect of food on Drug I (BCS class IV drug) in healthy subjects (modeling details are not provided in the table). This mechanistic absorption model included low aqueous solubility and permeability parameters. The model for healthy subjects predicts nonlinear PK of Drug I across a wide dose range. *In vivo* data under different fed/fasted conditions was used to validate the model. Though the simulation slightly under-predicted the impact of food effect, the model demonstrates the potential in using PBPK to quantitatively predict food effect. PBPK absorption models incorporating enhanced solubility and longer precipitation time under fed conditions have been used to predict positive food effect for a weak base drug with pH-dependent and limited solubility (31). Generally, when simulating food effect, longer gastric transit time, increased solubility caused by the secreted bile salt, and longer precipitation time may be put into the PBPK model to account for the changes caused by food intake (32–34). A number of recent publications have explored and demonstrated the utility of PBPK absorption model for predicting food effect (32–34).

In a separate NDA submission for Drug J (BCS class II drug, modeling details are not provided in the table), a PBPK absorption model integrated pH-dependent solubility, cellular permeability and disposition parameters obtained from a compartmental model. The applicant also conducted a sensitivity analysis on the stomach pH ranging from 0.5 to 8.0 to assess the effect of varying pH on the absorption of Drug J in humans. The predicted Fa remained ~ 1.0 across this pH range. In summary, model simulations suggested a lack of effect of elevating pH on the oral absorption of Drug J. The model was adequate for predicting negative pH-dependent effect. For drugs with pH-dependent solubility, qualitative prediction of pH-dependent drug interaction potential using a decisional framework has been published previously (35). To quantitatively predict the pH-dependent drug interaction potential, PBPK absorption models have been used as shown in the above example and other recent publications (30, 36), in predicting pH-dependent Drug-Drug Interactions. The recently published draft guidance for the evaluation of gastric pH-dependent drug interactions also

recommends that PBPK simulations can sometimes be used to further assess the potential for pH-dependent DDIs (37). Future work is warranted to provide further clarity in this regard.

GENERAL CONSIDERATIONS REGARDING THE USE OF PBPK ABSORPTION M&S FOR BIOPHARMACEUTICS ASSESSMENT

Considerations for PBPK Absorption Model Development

A general workflow for using PBPK absorption M&S for biopharmaceutics assessment is shown in Fig. 4. The diagram illustrates a general strategy for PBPK model development and lists some key model input parameters. Drug-dependent parameters include drug substance physicochemical properties such as solubility, API particle size, polymorphic form, and permeability, etc. Formulation-dependent inputs include precipitation time, supersaturation, and *in vitro* dissolution profiles. It is worth noting that some drug substance or formulation-dependent properties may not be directly incorporated into the model while their impact may be reflected by other input parameters, such as drug substance solubility, which may vary for different polymorphic forms; precipitation time, which may be affected by the excipients in the formulation and the manufacturing process; and *in vitro* dissolution data, which may also correlate with formulation and process (e.g., compression force/dwell time, granulate particle size, level of release controlling excipients, disintegrants, and lubricants). The system components include the parameters that describe the physiology of GI tract (e.g., secretion of gastric acid and bile, blood flow, gastric emptying time under fed and fasted conditions, pH in different sections of the GI tract, fluid volume in different sections of the GI tract) and other parts of the human anatomy, as well as abundance and distribution of drug-metabolizing enzymes and membrane transporters in various organ and tissue compartments. Population variability factors such as weight, genotype, age, and sex (intrinsic factors) may also need to be incorporated when needed (17, 38).

The general workflow provided in Fig. 4, together with the general strategy for mechanistic absorption model development provided by Zhang *et al.*(2), present a general process of model development, validation and application. Generally, model development in these scenarios considers the compartmental PK model and oral absorption model approach. For disposition compartmental PK model development, generally human PK data from intravenous or oral administration of the fastest dissolving formulation (e.g., an oral solution) are used as input data in the submitted models. The disposition PK parameters derived from IV data are widely considered the accurate representation of disposition properties, avoiding the complexity of *in vivo* drug release and absorption. If the IV data are not available, the data from oral solution and IR product are alternatively used, while the disposition PK parameters are additionally validated with more data to ensure the representation of true values of disposition parameters with no or minimum influence from absorption. The drug elimination phase can be modeled using total clearance, or detailed hepatic/renal clearance. If there is extensive first pass effect, hepatic clearance with enzyme information is often incorporated to predict the impact of metabolism in the GI tract and liver on bioavailability. The main enzyme information involved in the hepatic clearance is extrapolated from the *in vitro* data, while Vmax and Km serving as model input are often validated by additional human data from oral formulation with the consideration of between-subject metabolism level variability.

Thorough understanding of the drug physicochemical properties, drug release mechanism, as well as the ADME properties are considered to be key for developing a clinically meaningful and robust PBPK absorption model. Some commercial software provides a platform integrating the GI physiology with the input of drug substance physicochemical properties (e.g., pKa, solubility, partition coefficient, particle size, permeability) and formulation properties (e.g., dosage form and *in vitro* dissolution), by which the *in vivo* drug dissolution/release and regional absorption can be calculated. However, absorption model optimization is necessary in many cases. Fixing the parameters with high confidence and optimizing those parameters with high uncertainty have thus far proven to be a good approach for model optimization.

Considerations for How to Input Drug Product Quality Attributes

One of the advantages of the PBPK absorption model is the capability to integrate drug product physicochemical properties with the PK information for *in vivo* performance prediction. Therefore, appropriate input of drug product quality attributes is critical for utilizing the model for biopharmaceutics assessment. The recent publications also discussed various aspects of the development and validation of PBPK absorption or physiologically based biopharmaceutics models (PBBM) including appropriate model inputs (39–41).

Currently, the commercially available PBPK M&S software provides limited options for a direct incorporation of drug product quality attributes. For example, GastroPlus™ and SimCYP™ software emphasize a drug substance's properties such as pKa, solubility, LogD, permeability, and particle size, while only *in vitro* dissolution is considered for a drug product attribute as a direct model input. For APIs showing pH-dependent solubility, multiple solubility data at various pH conditions relevant to GI tract could be very helpful. Similarly, an API's solubility in biorelevant media (e.g., simulated gastric or intestinal fluid at fed/fasted conditions with/without bile salts) would be useful. Regarding the input of permeability parameters, the effective permeability, P_{eff}, converted from *in vitro* cell lines studies was generally used as a starting point in model building.

Current PBPK absorption models have a heavy reliance on the *in vitro* dissolution data as an input for predicting drug bioavailability, particularly for modified release products. To establish a robust PBPK model, the *in vitro* dissolution methods should be preferably bio-predictive. Otherwise, models have limited application for investigating the impact of Chemistry, Manufacturing and Controls (CMC) changes on the *in vivo* performance. There are several approaches for integrating *in vitro* dissolution data into the PBPK model: (1) direct input of *in vitro* data or after fitting the Weibull function; (2) use of *in vitro* data to fit z-factor to obtain the

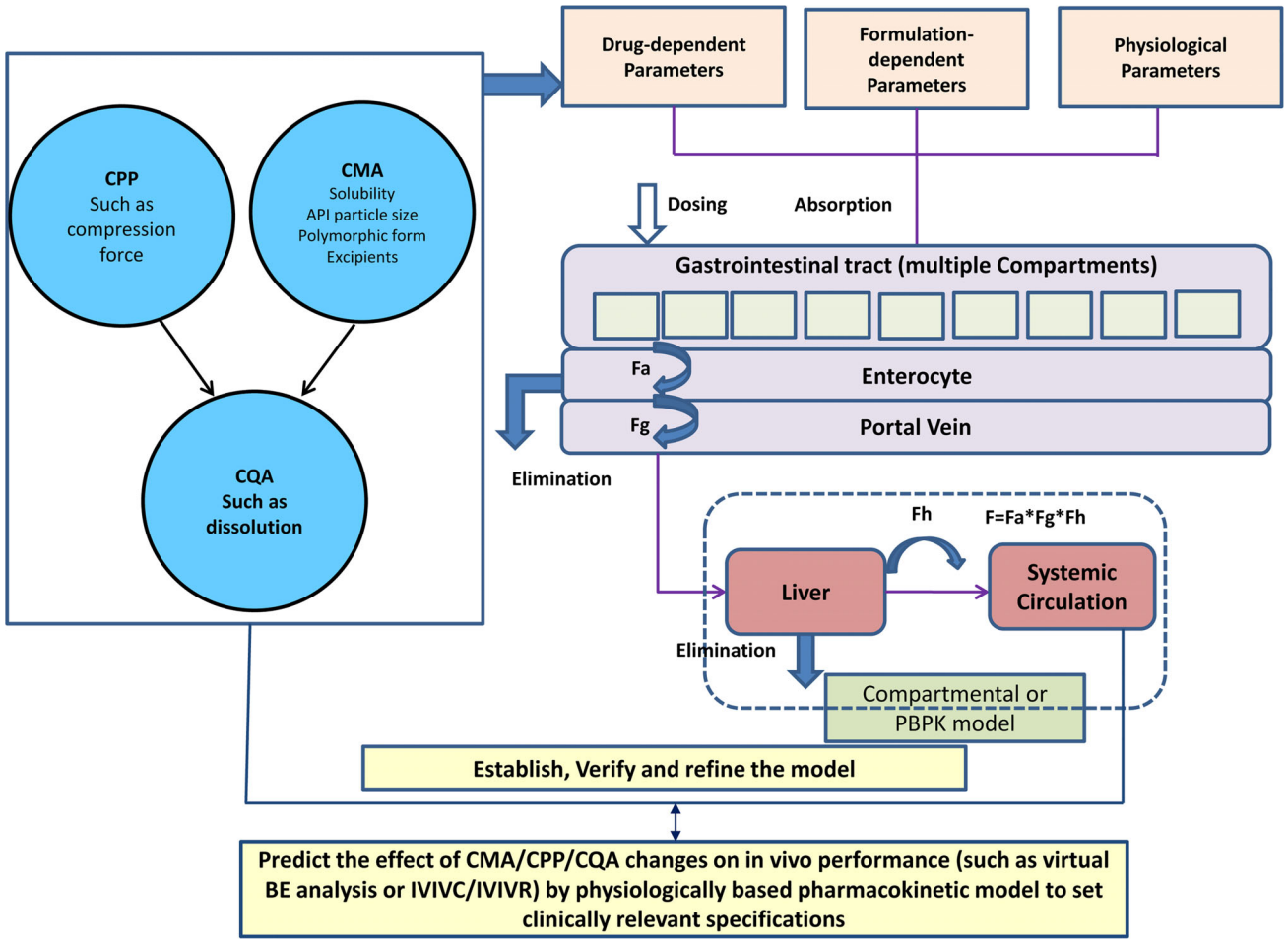

Fig. 4. General workflow for using PBPK modeling and simulation in biopharmaceutics assessment. Abbreviations: CPP, critical process parameters; CMA, critical material attributes; API, active pharmaceutical ingredient; CQA, critical quality attributes; F, oral bioavailability, Fa, fraction absorbed; Fg, bioavailability in the gut; Fh, bioavailability in the liver; BE, bioequivalence, IVIVC/R, in vitro in vivo correlation/relationship

drug release rate; and (3) generally, the dissolution models that are incorporated into the PBPK model include Weibull, Wang-Flanagan, z-factor, and Johnson models. When Johnson model was used, API particle size distribution or the Product-Particle Size Distribution (P-PSD) estimated based on the observed *in vitro* dissolution data could be utilized in the PBPK model (e.g., Drug B in Table II).

Based on the analysis on the 24 NDA PBPK submissions, five submissions used a z-factor dissolution model to obtain release rate and then evaluate potential formulation effect on their *in vivo* dissolution and absorption; four submissions used the Weibull model to describe dissolution profiles, or alternatively dissolution profiles were directly input to obtain a mechanistic IVIVC/IVIVR relationship between dissolution and *in vivo* drug exposure. Four submissions used PSD that would match the observed *in vitro* dissolution data or directly used the dissolution profiles in the model. For 11 submissions, solubility and particle size information and default Johnson dissolution model were used as an input in the PBPK model for simulating drug absorption. Generally, it is reasonable to select a dissolution model with lowest prediction error (PE) % and Akaike information criterion (AIC) value among all of the tested dissolution models. It should be noted that besides %PE and AIC, the coefficient of determination (R^2), adjusted coefficient of determination (R^2_{adjusted}), the correlation coefficient (R), the sum of squares of residues (SSR) and the mean square error (MSE) are also used to determine the adequacy of the models. However, it does not necessarily mean that all of the abovementioned indicators are needed for selecting the right dissolution model. PE% and AIC together with reasonable rationales are more often seen for dissolution model selection.

Considerations for Coupling Biorelevant Dissolution Data with PBPK Modeling

Solid oral dosage form dissolution behavior/performance can be affected by physiological conditions in the gastrointestinal tract. Dissolution in the gastrointestinal tract is within initial steps in the oral drug absorption process because only dissolved drug can permeate the mucosa at the absorptive sites. Thus, the solubility of the drug, its dissolution rate and permeability are crucial for its in vivo behavior. The use of biorelevant media, which mimic the stomach and small intestine physiological conditions, may enable a dissolution

test resulting in a better prediction accuracy of in vivo performance of the drug product, especially for drugs with poor solubility and/or with pH-dependent solubility. Examples of biorelevant dissolution media include fasted state simulated gastric fluid (FaSSGF), fed state simulated gastric fluid (FeSSGF), fasted state small intestinal fluid (FaSSIF), and fed state small intestinal fluid (FeSSIF) (42–44). Among the 24 NDA PBPK submissions, seven of them applied the dissolution data generated by a biorelevant dissolution method (41, 45). For example, a biorelevant dissolution method was developed for Drug D with the initial dissolution testing conducted in pH 4.9 buffer (simulating the fed stomach) for 1 hour followed by dissolution testing in FeSSIF (simulating the fed small intestine) for the rest of test (1.5 hours). The data were used to determine the dissolution rate (z-factor) of different batches, which were then used as an input in PBPK model to evaluate the effect of different dissolution rates on the *in vivo* exposure of Drug D. By coupling biorelevant dissolution data with PBPK model, it was concluded that differences in the dissolution rate evaluated within the model would not impact in vivo exposure of Drug D.

The dissolution data generated with biorelevant media coupled with PBPK modeling may provide better quantitatively and qualitatively accurate predictions of the in vivo performance of a drug product not only in an IR formulation containing poorly soluble drugs, but also in other formulations such as modified release formulations, depending on the drug characteristics and release mechanisms (40, 46). It has been investigated in the literature that for weak base drug products, a more complicated biphasic dissolution system with pH-shift may establish a better rank order of the absorption of prototype formulations in contrast to conventional dissolution testing, which may be due to its better capability of mimicking supersaturation and precipitation in the absorption of weak basic drug compounds (47, 48). For better prediction by coupling biorelevant dissolution testing with PBPK modeling, more studies are needed to translate the pH environment and hydrodynamic stresses the formulations encounter while they move along the GI tract into the design of appropriate in vitro dissolution test conditions.

Considerations for the Use of Parameter Sensitivity Analysis

As part of PBPK absorption model development, PSA is often used to validate the model's response and to identify the key model input parameters for *in vivo* performance prediction, such as diffusion coefficient, drug particle size, permeability, solubility, precipitation time, etc. The results of PSA support parameter optimization especially for critical parameters with high uncertainty. Alternatively, it is noted that with a validated PBPK absorption model, PSA provides useful information and confidence in the model if additional well-designed pilot PK studies are available to confirm the predicted trend by PSA. Moreover, PSA is potentially a powerful tool in Quality by Design (QbD) implementation such as (1) enhanced understanding of the drug product properties on the *in vivo* performance and (2) the quality-based risk assessment. Specifically, PSA can help in the identification of the CMAs and/or CPPs and establishment of subsequent control strategies.

Generally, PSA is performed two-dimensionally in which the PK parameters (such as Cmax and AUC) are changed by varying one parameter within a realistic range based on prior knowledge while keeping the other parameters unchanged. Two-dimensional PSA may not be sufficient especially when several parameters are uncertain (such as those obtained from *in silico* prediction or optimization). Multi-dimensional PSA has the advantage of tracking the interplay among uncertain parameters of interest; however, advanced modeling/programming skills may be needed. Simulations can be performed after creating combinations of a number of parameters of interest with several pre-defined levels. By plotting the results from multiple population simulations, the change of *in vivo* performance (e.g., Cmax and AUC) due to the interplay of several parameters can be described (49). Multi-dimensional PSA can be used to guide experiment design to obtain parameter values or further parameter optimization, thereby providing more confidence to the model. It is also very valuable in a QbD framework to investigate the interplay of multiple CQAs on the *in vivo* performance of the product.

Considerations for the Model Validation

Model validation is also very important for the evaluation of the model. In general terms, validation refers to an assessment of the model performance in comparison with observed in vivo data. PK data sets not used in model development such as different dosing regimens, fasted/fed conditions, and formulations/dosage forms, etc., have been found valuable for evaluating the predictive performance of the PBPK model. It is worth noting that the model validation should be purpose dependent. For instance, the multiple-dose or a higher single dose of an oral formulation may be helpful to verify the plausibility of the absorption model parameter set-up. In cases where enzyme information is incorporated into clearance, the PK data from subjects with poor metabolism may also be considered to confirm if the developed model can simulate PK differences due to varied metabolism levels. The model prediction performance on formulation changes such as particle size and *in vitro* dissolution rate has been seen in submissions to demonstrate evidence that the model reflects the impact of critical quality attributes on the *in vivo* performance. As PBPK absorption models are intended to be "fit-for-purpose," the adequacy of model validation depends on how appropriately the model can address the target question(s). In general, for addressing pharmaceutical development and quality issues, the adequacy of the model to predict the effect of model inputs on the PK performance of the studied drug product should be demonstrated by establishing a clear rank-order relationship between in vitro testing (e.g., in vitro release/dissolution) and in vivo PK study results (11). To increase confidence in the model, the recently published draft guidance (11) also recommends the sponsors to demonstrate the model's predictive performance based on PK data from batches exhibiting unacceptable bioavailability, in addition to those that exhibited acceptable bioavailability (compared to a target and/or reference product). Model validation acceptance criteria

Table IV. Limitations/Shortcomings Observed in Physiologically Based Pharmacokinetic Absorption Modeling and Simulations Contained in Regulatory Submissions from Biopharmaceutics Perspective

Item	*In vitro* input data	*In vivo* input data	Model development	Model validation
Limitations/ shortcomings observed in PBPK absorption model	Lack of bio-predictive dissolution data The sources of the model input parameters were not reasonably clarified or clearly discussed The range of the z-factor for sensitivity analysis is not reasonably justified with the consideration of the batch variabilities Solubility input is not clinically relevant	Lack of availability of clinical data (e.g., intravenous data) to support the simulation results Lack of reliability for parameter estimation Uncertainty of tissue blood partition coefficients for different organs, luminal and enterocyte concentrations Lack consideration of population variabilities in physiological parameters	Lack of justification for parameters used in setting up the PBPK model Improper selection of dosage form Dissolution model selection is not reasonable Lack of reasonable justification when PBPK model predicted failing BE while biorelevant dissolution test demonstrates similarity Lack of consideration of saturation of renal and hepatic transporters/ enzymes Lack of justification when the PBPK model predicted that Cmax and AUC values were higher for a batch with a slower dissolution profile. For establishing mechanistic IVIVC/IVIVR, the model was constructed using only one release rate formulation instead of at least two to three release rates Make wrong assumption such as assuming a 100% bioavailability without metabolism in gastrointestinal tract and liver	Lack of information on method validation criteria Lack of sufficient *in vivo* study data to validate the PBPK model; Validation is performed with the same batch as that used for model establishment Lack of sufficient validation, e.g., the PBPK model is not challenged by prediction for a non-BE batch when validation dataset is limited

Notes: *BE*, bioequivalence; *IVIVC/IVIVR*, in vitro in vivo correlation/relationship; *Cmax*, maximum drug concentration; *AUC*, area under the curve

should be established a priori and the criteria should be appropriate for the specified application. For instance, the acceptance criteria for a mechanistic IVIVC model to support biowaiver should comply with the criteria provided in the guidance for industry Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations (20).

Regarding modeling procedures, in addition to model development, validation/modification, and application in a step-wise manner, from a biopharmaceutics perspective, the formulation and manufacturing information for all the batches or formulations used in the PBPK model development and validation provide additional information. The evaluation of the PBPK model is based on the totality of the supportive data and relevant information, especially the demonstration of model predictability.

Considerations for the Use of Virtual BE Analysis

Virtual BE trial simulations have been used to verify the proposed ranges for product CMAs, CPPs, and CQAs and/or other formulation variables, in which all possible variants (of input parameters) were incorporated simultaneously using a stochastic simulation approach by randomly sampling parameters from pre-defined distributions. Crossover trial design with a BE comparison (90% CI of the test-to-reference geometric mean ratio of Cmax and AUC fall within and 80–125% is considered BE) are used to compare the virtual batch with pivotal BA/BE batches with targeted efficacy and safety profiles. When virtual BE simulation is conducted, the following should be considered: (i) the estimated intra- and intersubject variability for PK parameters (such as Cmax and AUC) should be representative of the observed intra- and inter-subject variability; (ii) the number of subjects for virtual BE trials should be justified and comparable to in vivo BE studies; and (iii) the number of virtual BE trials used to estimate the probability of concluding BE should be justified (11).

Future Direction: Challenges and Opportunities

The pharmaceutical industry utilizes PBPK absorption M&S for new drug candidate and/or formulation selection from early drug discovery stage through post-approval lifecycle quality management (50). The FDA is encouraging the use of PBPK absorption M&S to support application for regulatory decision making regarding clinical pharmacology assessment for predicting pH-dependent DDI and biopharmaceutics assessment for quality changes as well as BE evaluation (17, 51–53). There are still many areas for improvement that can to be addressed to maximize the utility of PBPK absorption models to predict oral drug absorption. From a model development perspective, an improved understanding of GI tract physiology, especially

in the lower small intestine and colon is needed. Subject variabilities in GI physiology also need to be better understood to significantly increase the ability to predict the inter-(and potentially intra-) subject variability of drug exposure, such as transition time, pH, fluid dynamics (volume), GI wall enzyme/transporter abundance and regional distribution, fasted/fed condition, or the influence of disease status. By taking account of the realistic variabilities of GI physiology, the virtual BE trials can be more meaningful and have more practical applications.

The confidence of using PBPK absorption M&S also depends on the availability and quality of the *in vitro* and *in vivo* data for establishing the model, and on the predictive performance of the model. Mechanistic PBPK absorption models are very valuable in predicting the impact that changes on the critical quality attributes (e.g., dissolution) may have on the *in vivo* performance. However, their applications are limited by the lack of "quality" of the data, such as bio-relevant solubility, dissolution profiles, permeability, and particle size changes during the possible precipitation process or limited by the lack of confidence in drug/formulation-dependent or system-dependent parameters. The limitations and shortcomings observed in PBPK absorption M&S in regulatory submissions are summarized in Table IV.

Despite these challenges, PBPK absorption M&S has great advantages over conventional methodology in risk assessment, supporting the establishment of clinically relevant criteria on the basis of evaluating *in vivo* "sameness" of formulation. For example, the generally accepted dissolution criteria of mean ± 10% range for some orally administered ER product is set based on the assumption that the method is discriminating. As such, without understanding the relationship between the quality attributes and the clinical outcome, drug product specification limits may be too wide, unnecessarily tight, or completely irrelevant to clinical performance (25). In this context, there are opportunities in developing bio-predictive dissolution method, setting clinically relevant drug product specifications based on PBPK M&S, and conducting risk assessment of scale-up and post-approval changes (SUPAC) on *in vivo* drug exposure by evaluating virtual bioequivalence. In addition, with bio-predictive dissolution testing, physiologically based IVIVC may result in an increased IVIVC success rate compared with conventional IVIVC (22, 25). Although the development of a bio-predictive*in vitro*dissolution/release method remains a challenge, bio-predictive dissolution methodologies have been continuously explored by using biorelevant media/conditions and establishing IVIVC and have led to promising outcomes.

Based on the purpose and application of the PBPK models, the complexity of the model and model parameters may be different. By overcoming the limitations and incorporating the "predict, learn and confirm" strategy, PBPK absorption M&S is likely to be increasingly used in future biopharmaceutics and clinical pharmacology assessment.

CONCLUSIONS

The use of PBPK absorption M&S in NDA submissions with the purpose of supporting CRDPS and patient-centric assessment of quality such as performing risk assessment on the effect of changes in CMAs, CPPs, and CQAs on drug exposure, assessing biowaiver requests, evaluating food effect and pH-dependent drug interactions has been increased due to increased knowledge and software availability. The cases provided in this article highlight the utility of the PBPK absorption M&S in the above areas. It is envisioned that a broader use of PBPK absorption M&S in drug product development would enable a patient-centric assessment of drug quality and safe and effective use of drug products.

DISCLAIMER

Dr. Ping Zhao participated this work while he was an employee at US FDA. The findings and conclusions contained within are those of the authors and do not necessarily reflect the official positions or policies of the Bill & Melinda Gates Foundation.

FUNDING

The project is partially supported by FDA MCMi funded Oak Ridge Institute for Science and Education (ORISE) Fellowships. The authors thank Drs Da Xu and Huong Moldthan on collecting some parts of the PBPK data included in regulatory submissions. Drs Da Xu and Huong Moldthan were supported by an appointment to the Research Participation Program at CDER, administered by ORISE through an interagency agreement between the US Department of Energy and the FDA.

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